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BILIARY CIRRHOSIS

BILIARY cirrhosis will be considered under two distinct heads: (i) Hypertrophic biliary cirrhosis, and (ii) obstructive biliary cirrhosis.

HYPERTROPHIC BILIARY CIRRHOSIS

It is sometimes spoken of as "hypertrophic cirrhosis." This is likely to lead to confusion, as there are several other kinds of large cirrhotic livers; in common or portal cirrhosis the organ is often much enlarged, a fatty cirrhotic liver is of very considerable size, and the pigmented cirrhotic liver in haemochromatosis is also entitled to the adjective hypertrophic. The term "hypertrophic cirrhosis" should therefore be given up.

Definition.—The disease is characterised by chronic jaundice, periodic ~~febrile attacks~~, absence of ascites, enlargement of the liver and spleen, and by its preference for young persons. There is no gross obstruction in the larger bile-ducts, and histologically the cirrhosis is more unilobular than in portal cirrhosis.

attacks of
abdominal
pain and
fever

History.—Although the condition was recognised by Requin¹ in 1846, by Todd² eleven years later (1857), and by Hayem in 1874,³ it attracted little attention until Hanot⁴ (1875) sharply struck out the disease in his thesis on "Hypertrophic Cirrhosis with Chronic Jaundice."

Hanot's thesis was based on 15 cases, 4 of which he had observed during life; in 3 of the 4 a necropsy was obtained.

In 1893 Kiener⁵ suggested that the disease should be called Hanot's disease. Since then somewhat different though allied forms of hypertrophic biliary cirrhosis have been described in France (*vide* p. 310), and discussion has arisen as to the channel by which the cause of the disease reaches the liver. For some years the opinion has been growing that the description given by Hanot was too crystallised, and that few cases conform to the rigid type he erected. It has also been suggested that the symptoms and signs do not correspond to any one anatomical change in the liver, but may be associated with various forms of cirrhosis. Oertel⁶ denies that the morbid appearances are sufficiently characteristic to justify the recognition of a special form; Meyer⁷ takes the same view, and some writers in this country consider that no real distinction

¹ Requin. *Pathologie méd.*, tome ii, p. 748.

² Todd. *Med. Times and Gaz.*, 1857, xv, 571.

³ Hayem. *Arch. de physiol. norm. et path.*, Paris, 1874, 2. s., i, 126.

⁴ Hanot. *Thèse de Paris*, 1875.

⁵ Kiener. *Semaine méd.*, Paris, 1893, xiii, 345.

⁶ Oertel. *Arch. Int. Med.*, Chicago, 1908, i, 394.

⁷ Meyer. *München. med. Wchnschr.*, 1908, lv, 2276.

can be drawn between portal and hypertrophic biliary cirrhosis. Further, the clinical features of hypertrophic biliary cirrhosis occur in cases which on necropsy shew portal cirrhosis. This discrepancy between the clinical picture and the morbid changes is probably due to the fact that cirrhosis, wherever it begins, will after a time spread and lead to a mixed cirrhosis. Thus, there is a special tendency for changes presumably beginning in the small bile-ducts to become complicated in course of time by those of portal cirrhosis. After much consideration of the question I have come to the conclusion that there is an essential difference, both clinically and pathologically, between portal and hypertrophic biliary cirrhosis, and that Hanot and the French school are fully justified in their contention. No doubt transitional forms between the two types of cirrhosis occur, just as they do between the arteriosclerotic (granular) kidney and that of chronic parenchymatous nephritis (large white kidney); but it would be incorrect to assume that they are different manifestations of the same process. Although different types exist, it is advisable to give an inclusive description of the disease as a whole, and to draw attention to the varieties which may occur.

Different Forms of Hypertrophic Biliary Cirrhosis.—A number of cumbrous names have been coined to distinguish varieties of the disease. These varieties depend on differences in the degree of the splenic and hepatic enlargement, and on the relationship between the enlargement of the two organs, both in size and in the date of appearance. The following forms were described by Gilbert,¹ Chauffard,² and Lereboullet. *Ordinary form of hypertrophic biliary cirrhosis*, described by Hanot, in which the liver and spleen are both enlarged. *Splenomegalic form*, in which the splenic enlargement is the predominant feature. *Hypersplenomegalic form*, in which the spleen is actually larger than the liver. *Metasplenomegalic form*, in which splenic enlargement precedes any manifest change in the liver. *Hepatomegalic* or *microsplenomegalic form*, in which the enlargement of the liver is the prominent feature; the spleen may not be enlarged (asplenomegalic form). *Presplenomegalic form*, in which the enlargement of the liver precedes that of the spleen. *Atrophic biliary cirrhosis*, in which the liver is small. A special *juvenile type* with great splenic enlargement was described by Gilbert and Fournier.³

In the cases in which the spleen is considerably enlarged before the liver is noticed to be affected—metasplenomegalic hypertrophic biliary cirrhosis—Chauffard believes the hepatic cirrhosis to be due to poisons manufactured in the spleen, and that the disease is a different one from the ordinary type. There is a gradual transition from the less marked examples of metasplenomegalic biliary cirrhosis to Banti's disease or splenic anaemia with a terminal cirrhosis. Cases without jaundice, "*Cirrhose biliaire anictérique*," have also been described.

¹ Gilbert. *Semaine méd.*, Paris, 1900, xx, 154.

² Chauffard. *Ibid.*, 1900, xx, 176.

³ Gilbert et Fournier. *Compt. rend. Soc. Biol.*, 1895, xlvii, 419.





Some Forms of Disease possibly allied to Hypertrophic Biliary Cirrhosis.—As in many other diseases, there are less characteristic cases ("fruste" or larval) which present some of the features of biliary cirrhosis, but are incomplete and wanting in others. Thus, as just mentioned, there may be transitional cases between splenic anaemia and hypertrophic biliary cirrhosis. Barlow and Shaw¹ published two cases of recurrent attacks of jaundice and abdominal crises with enlargement of the liver and spleen, in a mother and son, which seem to form a connecting link between hypertrophic biliary cirrhosis and chronic splenic anaemia. Chronic haemolytic jaundice (*vide* p. 537) also resembles biliary cirrhosis, especially the metasplenomegalic form in which the spleen is enlarged before the liver.

Incidence.—Genuine ~~cases of~~ hypertrophic biliary cirrhosis ^{is} ~~are~~ distinctly rare; this contrasts with the frequency of portal cirrhosis. The rarity of the disease is perhaps not fully recognised since cases of ordinary cirrhosis with large livers but without persistent jaundice are not infrequently confused with it.

Etiology.—*Age.*—It is commonest between the ages of twenty and thirty and is rare after forty, thus again contrasting with common cirrhosis in which the average age is about forty-eight years. A considerable number of cases occur in young children (Gilbert and Fournier's juvenile form).

Sex.—In children the incidence of the disease falls fairly equally on the two sexes. In 22 cases collected by Morley Fletcher,² including Gilbert and Fournier's 7 cases, there were 13 male and 9 female children. In adult life males are more often attacked. In Schachmann's³ 26 cases only 4 were females.

Heredity.—The disease may be found in more than one generation (Boix, Boinet), but probably this depends on the surroundings more than on direct heredity. The disease is sometimes familial or met with in several members of the same family when exposed to the same conditions.

Finlayson⁴ described 3 cases in one family. Dreschfeld⁵ recorded the disease in two brothers, and Osler⁶ had a similar experience in America. Boix,⁷ Boinet,⁸ and Hasenclever⁹ also published similar groups of cases. In Brahmin infants in India a form of cirrhosis described as biliary is very common, and is especially apt to attack members of the same family. But these cases are not the same as Hanot's disease, and may be kala azar. The condition is referred to elsewhere (p. 335).

¹ Barlow and Shaw. *Trans. Clin. Soc., Lond.*, 1902, xxxv, 155.

² Fletcher, H. Morley. *System of Medicine* (Allbutt and Rolleston), 1908, iv, part i, 185.

³ Schachmann. *Thèse de Paris*, 1887.

⁴ Finlayson. *Glasgow Hosp. Rep.*, 1899, ii, 39.

⁵ Dreschfeld, J. *Med. Chron.*, 1896, N.S., v, 19.

⁶ Osler. *Practice of Medicine*, p. 561, 6th ed., 1905.

⁷ Boix. *Compt. rend. Soc. Biol., Paris*, 1898, l, 297.

⁸ Boinet. *Arch. gén. de méd.*, 1898, clxxxi, 358; and 1903, cxci, 362.

⁹ Hasenclever. *Berlin. klin. Wehnschr.*, 1898, xlv, 997.

In other members of the same family who have no symptoms of disease the spleen may be enlarged (Boix, Boinet); this is analogous to the loss of knee-jerk in apparently healthy members of a family containing some children affected with hereditary ataxia.

In one family the father and two children had fully developed hypertrophic biliary cirrhosis, and three other children had big spleens (Boinet).

Lereboullet¹ described the "cholæmic family," the members of which are supposed to be specially susceptible to infection of the bile-ducts, much in the same way as other families are rheumatic or tuberculous. The subjects of this diathesis are probably more likely to have hypertrophic biliary cirrhosis than ordinary persons (*vide* p. 40).

Alcoholism.—Although the antecedents of patients with hypertrophic biliary cirrhosis sometimes include heavy drinking, there is no reason to regard alcoholism as related to the disease in the same way as it is to common cirrhosis. Alcoholic excess may dispose to infection by reducing the resisting power of the body as a whole and of the liver in particular. Of the two brothers recorded by Dreschfeld, one was a hard drinker while the other was temperate. Boix put forward the view that the infection is introduced into the body in water; and it has been thought that cold and damp houses favour the occurrence of the disease.

Malaria, etc.—In some instances malaria has preceded the onset of the disease, but in the majority of instances this can be ruled out of court. Géraudel² revived Lancereaux's view of 1871—that the signs and symptoms ascribed to the disease are malarial in origin.

There is no reason to believe that syphilis or tuberculosis plays any special part in the causation of the disease. In a few cases it has been noticed to develop after typhoid fever (Boinet, and Gilbert and Lereboullet³). Odon⁴ collected 9 cases; as *B. typhosus* causes cholecystitis and cholangitis, it appears probable that it may produce analogous changes in the small intrahepatic ducts and that the infective process once started may become mixed and shew other microbes such as *B. coli*.

Pathogeny.—Hanot originally regarded the initial lesion as a catarrhal inflammation of the small bile-ducts. In favour of an infective origin for this cholangitis the following points may be urged: the frequency of fever; the considerable splenic enlargement, which indeed may precede or be more marked than that of the liver; and glandular enlargement, not only in the portal fissure, but occasionally in more distant parts of the body.

There are two views as to the path by which the infective or toxic agent reaches the liver: (a) A descending cholangitis, or an inflammation beginning in the small intrahepatic bile-ducts due to an irritant reaching

¹ Lereboullet. *Les Cirrhoses biliaires*, Thèse de Paris, No. 180, 1902.

² Géraudel. *Thèse de Paris*, 1902.

³ Gilbert et Lereboullet. *Compt. rend. Soc. Biol.*, Paris, 1905, lvi. 706.

⁴ Odon. *Thèse de Paris*, 1905-6, No. 77.

1) though Castaigne has suggested
a syphilitic origin.

Experimentally manganese salts which are mainly excreted in the bile produce
biliary cirrhosis (M. Findlay) and it is interesting to note that the clinical
symptoms of chronic manganese poisoning resemble those of lenticular degeneration (vide p.)
Casamajor has reported biliary cirrhosis in a fatal case of manganese poisoning in man.

Castaigne. La clinique, Par., 1913, viii, 661.

Findlay, M. Brit. Journ. Exper. Path., London 1924, v, 92

Casamajor. Kober and Hanson's Occupational Diseases and Vocational Hygiene, 1916



them by the blood-stream, as in experimental toluylenediamine poisoning. The changes in the liver and spleen would then be the local results of a general toxæmia or infection. In cases in which the spleen becomes manifestly enlarged before the liver (metasplenomegalic biliary cirrhosis), the liver is probably more resistant to infective or toxic influences than in the ordinary cases of biliary cirrhosis. (b) That hypertrophic biliary cirrhosis is due to a local infection of the bile-ducts from the duodenum—an ascending cholangitis—by bacilli of the colon group (Gilbert and Fournier,¹ Potain²). The enlargement of the spleen is regarded as secondary to the local infection of the liver and due to micro-organisms or their poisons absorbed from the infected bile-ducts. In some cases in which the gall-bladder has been drained, micro-organisms such as the *Bacillus coli* and *Diplococcus pneumoniae* have been found in the biliary tract; there may be some question whether all the 17 cases included in Greenough's³ list of operations were genuine examples of hypertrophic biliary cirrhosis, but the marked success in 13 of the cases is in favour of an ascending infection (*vide* p. 326).

Against the view that it is an ascending infection might be urged the comparative infrequency of antecedent dyspepsia, the absence of duodenitis at necropsies, and that the spleen may be enlarged before the liver, and before there is any jaundice. Further, if the condition were due to an ascending infection from the duodenum, the pancreatic duct should also become infected, and as a result chronic interstitial pancreatitis with increase in the size of the head of the pancreas should occur.

Guillain⁴ described such a condition, under the name of "Sclérose hépatopancréatique hypertrophique avec hypersplénomégalie," in a temperate woman aged fifty-two years; there were hypertrophic biliary cirrhosis and enlargement of the pancreas to double its normal size. He regarded the condition as due to an ascending infection.

In biliary cirrhosis there is some chronic pancreatitis, but the pancreas is not enlarged (Lefas⁵).

Possibly some of the forms of hypertrophic biliary cirrhosis are like Guillain's type, due to an ascending infection, but the majority are, like scarlatinal nephritis, due to a hæmic infection or intoxication of a chronic nature. This is conveyed by the hepatic artery; for the cirrhosis induced by poisons arriving by the portal vein is nearly always multilobular.

Bacteriology.—Although anticipated, no microbic cause has yet been satisfactorily established. The colon bacillus has been found in blood withdrawn by puncture from the liver during life and subsequently in the liver and spleen in the same case (Gilbert and Fournier). But

¹ Gilbert et Fournier. *Compt. rend. Soc. Biol.*, 1897, xlix, 692. *l.c.*

² Potain. *Semaine méd.*, 1896, xvi, 101.

³ Greenough. *Am. Journ. Med. Sc.*, 1902, cxxiv, 979.

⁴ Guillain. *Rev. de méd.*, 1900, xx, 701.

⁵ Lefas. *Arch. gén. de méd.*, Paris, 1900, clxxxv, 539.

further evidence is necessary before the colon bacillus can be regarded as the specific cause. Hayem,¹ in his cases of chronic infective jaundice with splenic enlargement and exacerbations, which is perhaps allied to hypertrophic biliary cirrhosis, found the *Diplococcus pneumoniae* in blood aspirated from the spleen during life. A diplococcus was also described by Kirikoff.²

Morbid Anatomy.—The liver is uniformly enlarged; but one lobe, usually the left, may be more affected than the other. It usually weighs from 80 ounces upwards, even to eight pounds or more.

In very exceptional cases the liver is described as smaller than natural—"atrophic biliary cirrhosis." It does not seem clear that Weber's³ case, in which the liver of a girl aged fourteen years was hobnailed and weighed 26½ ounces, was not one of portal cirrhosis.

Perihepatitic adhesions uniting the liver to the diaphragm are not uncommon, but otherwise the surface is fairly smooth, and is at most finely granular. It does not present the gnarled and hobnailed appearance of common cirrhosis. In long-standing cases secondary portal (multilobular) cirrhosis supervenes and the surface may be irregular. It is of a dark-green colour and on section is firmer than natural and has an aspect like granite, due to the fine mesh of the fibrosis.

The portal vein, hepatic artery and veins are normal. The gall-bladder contains bile and is usually healthy, though its walls are sometimes thickened. The larger bile-ducts appear normal. As there is cholangitis it is remarkable that bilirubin-calcium calculi are not more often present in the ducts. Gall-stones have been found in some cases, but are a secondary formation; as they are not constant, they cannot be regarded as the cause of the cirrhosis.

Microscopic Appearances.—The liver shews fibrosis, which in the earlier stages is unilobular and tends to surround each lobule, much in the same way, though not so diagrammatically, as in a pig's liver. In the early stages the unilobular arrangement is well seen. But in long-standing cases the fibrosis is often irregular and there is usually multilobular cirrhosis. This confusing picture no doubt accounts for the difficulty experienced by many writers in accepting hypertrophic biliary cirrhosis as a distinct pathological type. I regard this multilobular cirrhosis as a secondary change, which may very plausibly, on Chauffard's hypothesis of splenogenous cirrhosis (*vide* p. 188), be referred to the action of poisons manufactured in the enlarged spleen and conveyed to the liver by the portal vein. In cases fatal from accident or from some intercurrent disease the unilobular cirrhosis, described by Hanot, may be seen unobscured by the secondary multilobular cirrhosis which supervenes in long-standing cases.

¹ Hayem. *Presse méd.*, Paris, 1898, i, 121.

² Kirikoff. *St. Petersb. med. Wchnschr.*, 1900, xvii, 353.

³ Weber, F. P. *Trans. Path. Soc.*, Lond., 1896, xli, 71.





The connective tissue of the unilobular cirrhosis is delicate and fibrillar, somewhat like neuroglia, and has an open structure. In some parts it invades the lobules and becomes unicellular; Kaufmann¹ regards this as characteristic of Hanot's cirrhosis. As compared with the fibrosis of multilobular cirrhosis it is much less dense, but is more intimately related to the lobules and cells of the liver. The delicate connective tissue contains branching anastomosing elastic fibres, which invade the lobules and form a fine network between the cells. The elastic tissue is derived especially



FIG. 39.—Unilobular cirrhosis with some invasion of the lobules by delicate connective tissue. The liver cells are shrunken from the effects of the hardening agent (absolute alcohol). $\times 25$.

from the sheaths of the bile-ducts (Carnot and Amet²), and may also spread in from the capsule, where it is normally present. There is less newly formed elastic tissue in biliary cirrhosis than in portal cirrhosis (Flexner³). The small bile-ducts are surrounded by small round cells and fibrosis; some shew obliterative cholangitis, others are dilated (Lereboullet⁴). The bile capillaries often contain plugs of inspissated bile.

Pseudobile Canaliculi.—Around the margins of the lobules and in the fibrillar interlobular connective tissue there are columns of small,

¹ Kaufmann. *Lehrbuch d. spez. path. Anat.*, 1907.

² Carnot et. Amet. *Arch. de méd. expér. et d'anat. path.*, Paris, 1906, xviii, 763.

³ Flexner. *Univ. Med. Mag.*, Phila., 1900, xii, 614.

⁴ Lereboullet. *Les Maladies du foie et leur traitement*, p. 325, 1910, Paris.

deeply staining cells. The cells, which surround a potential lumen, are either cubical or elongated so as to lie parallel to the long axis of the column. Occasionally the lumen is dilated, and, though ordinarily empty, may contain minute biliary calculi. The columns of cells twist and branch in the neighbourhood of the lobules. Though they are particularly well marked in hypertrophic biliary cirrhosis, and are only exceptionally absent in that disease, their presence is not pathognomonic of it, for they are met with in many morbid conditions of the liver, such as portal cirrhosis, abscess, acute yellow atrophy, gumma, and tuberculosis, which tend to destroy the liver cells or interfere with their functional activity. The histological appearances of the so-called new bile-ducts are the same in all these various conditions and differ from normal bile-ducts in that there is either a complete absence of a covering of elastic fibres or a very imperfect development of this tissue around them (Flexner). A great deal of discussion has taken place as to their nature and origin (*vide* p. 205).

Hanot and Gastou¹ regard these so-called new bile-ducts as the first results of irritation of the liver cells, and explain their frequency in hypertrophic biliary cirrhosis as a direct consequence of the exacerbations in the course of the disease.

Hanot insisted that the liver cells are for a long period extremely well preserved, and when the patient dies from some other cause, do not shew the fatty and degenerative changes seen in portal cirrhosis. In many cases acute degenerative or toxic changes occur shortly before death. The integrity of the liver cells has been disputed, and it has been asserted that this statement is based on examination of cells shewing attempts at regeneration (Kaufmann²).

Relation of Banti's Disease to Hypertrophic Biliary Cirrhosis.—In chronic splenic anaemia a terminal multilobular cirrhosis may supervene, probably as the result of poisons manufactured in the spleen; this is called Banti's disease. Hypertrophic biliary cirrhosis is essentially unilobular, but in the late stages a secondary multilobular cirrhosis, probably of splenic origin and like that of Banti's disease, may supervene.

The *spleen* is much larger than in portal cirrhosis; its weight commonly varies between 15 and 40 ounces, but may be considerably more. The organ may thus weigh twice to six times its normal weight, whereas the liver is seldom more than twice or three times its ordinary weight. The spleen is therefore relatively heavier than the liver. In some rare cases the spleen is absolutely bigger and heavier than the liver; this is more likely to be met with in children than in adults. To this condition Gilbert³ applied the term hypersplenomegalic hypertrophic biliary cirrhosis.

¹ Hanot et Gastou. *Compt. rend. Soc. Biol.*, Paris, 1893, xlv, 741. /112

² Kaufmann. *Lehrbuch der spez. path. Anat.*, 1907.

Gilbert. *Semaine méd.*, Paris, 1900, xx, 124.





In F. Taylor's¹ case the spleen weighed $87\frac{1}{2}$ ounces and the liver 40 ounces, and in a case recorded by Milian and Landrieux² the spleen weighed $94\frac{1}{2}$ ounces and the liver $65\frac{1}{2}$ ounces. In a very chronic case of hypertrophic biliary cirrhosis, in which jaundice, enlargement of the spleen down to the umbilicus, and clubbing of the fingers were noticed seven years before death, the liver weighed 65 ounces and the spleen 77 ounces (Roger Smith³).

There are frequently perisplenic adhesions from local peritonitis and thickening of the capsule with local exaggerations of this change or lamellar fibromas. In uncomplicated cases, *i.e.* when death is not due to acute infection, the spleen is firmer than natural.

Microscopically there is fibrosis, with distension of the sinuses with blood. The Malpighian bodies in an early stage are hyperaemic; later they may undergo fibrotic atrophy, a process which occurs in other chronic toxæmias, and has been obtained experimentally by Pilliet⁴ as a result of poisoning by metatoluylenediamine, paraphenylene, and nitrate of sodium. There is also some endothelial hyperplasia in the pulp.

The *lymphatic glands* in the portal fissure are usually enlarged, but are so soft that they do not press on the bile-ducts. They are dark in colour and oedematous; and microscopically shew fibrosis and pigmentation. The pigment is probably derived from destruction of the red blood corpuscles (haemolysis), but differs from the pigmentation of general haemochromatosis in not involving the liver and spleen. The lymphatic glands around the pancreas may also be similarly affected, and glandular enlargement has been noted in the mesentery, groin, axilla, mediastinum, and neck (Popoff⁵).

The *alimentary canal* is usually free from signs of past inflammation. Hanot noted that the duodenum in the region of the biliary papilla was not affected by catarrh; Debove's experience, however, is rather in the opposite direction.

The *pancreas*, as a rule, is not increased in size or weight, but it is far from normal. It is indurated and may be united by adhesions to neighbouring organs. There is an intimate fibrosis of an embryonic type spreading from the ducts. In addition to this form of fibrosis there are some proliferation of the cells lining the ducts and fatty degeneration of the cells of the acini (Lefas⁶). In exceptional cases, as in Guillain's⁷ hypertrophic cirrhosis of the liver and pancreas with extreme splenic enlargement, the pancreas may be enlarged.

The *kidneys*, except for bile-staining, are healthy and may shew hypertrophy (Milian⁸). All the organs are bile-stained.

Clinical Picture.—The *onset* may be gradual, and before jaundice

¹ Taylor, F. *Guy's Hosp. Rep.*, 1900, liv, 5.

² Milian et Landrieux. *Semaine méd.*, Paris, 1900, xx, 124.

³ Smith, H. Roger. *Trans. Clin. Soc.*, Lond., 1898, xxxi, 264.

⁴ Pilliet. *Compt. rend. Soc. Biol.*, Paris, 1894, xlv, 331.

⁵ Popoff. *Sovrem. klin.*, St. Petersburg, 1895.

⁶ Lefas. *Arch. gén. de méd.*, Paris, 1900, clxxxv, 539.

⁷ Guillain. *Rev. de méd.*, Paris, 1900, xx, 701.

⁸ Milian. *Bull. Soc. Anat.*, Paris, 1901, lxxvi, 323.

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sets in malaise, loss of strength, and, in some cases, dyspepsia, abdominal distension or pain, and pruritus may be noticed. Occasionally pain is first noticed in the left hypochondrium, and physical examination shews that there is considerable enlargement of the spleen. Usually, however, the patient first seeks medical advice after the appearance of jaundice. The onset of jaundice may be almost imperceptible; in other cases it may be sudden and be accompanied by gastro-intestinal disturbance, thus resembling catarrhal jaundice, or be accompanied by abdominal pain and some fever, so as to imitate an attack of intermittent hepatic fever due to a calculus in the common bile-duct.

Gilbert¹ described three modes of onset: (i) The hepatic, with jaundice and pain over the liver; (ii) the gastro-intestinal, with loss of appetite, sickness, diarrhoea, and abdominal pain; and (iii) the splenic, with pain in the left hypochondrium and enlargement of the organ.

The *course* of the disease is characteristically slow. For a considerable time—often for years—the general health is fairly maintained in spite of persistent jaundice. At intervals crises or attacks of abdominal pain with fever and increase in the jaundice occur; these exacerbations, like those in pernicious anaemia and in Addison's disease, lower the general health and nutrition. The periodic exacerbations become more frequent and the disease makes steady though slow progress, wasting and loss of strength appear, and the general state becomes very unsatisfactory. Death may be due to intercurrent disease, to the gradual development of complete hepatic insufficiency and the resulting toxæmia, or during one of the exacerbations acute degenerative changes in the liver cells may lead to icterus gravis. In the last event jaundice deepens, delirium and nervous symptoms appear, and a "typhoid" or comatose condition ushers in death.

Symptoms.—The tongue is often furred, but may be clean for long periods. The appetite is sometimes poor, but is frequently normal and in some instances has been very excessive. There is not the marked distaste for fatty food met with in ordinary obstructive jaundice. Dyspepsia is much less frequent than in portal cirrhosis. Hayem stated that hyperacidity is constant, but Kirikoff's² results were entirely opposed to this. Nausea and vomiting are occasionally present. Haematemesis is rare; it may occur late in the disease as the result of secondary portal cirrhosis and even prove fatal. Milian³ recorded fatal haematemesis from an oesophageal varix. Attacks of diarrhoea on slight provocation are not uncommon. The motions contain stercobilin, though from intercurrent catarrhal jaundice the stools may be temporarily pale. In 26 cases collected by Schachmann⁴ the faeces were colourless in only two. A

The abdomen is prominent and distended, especially in the upper

¹ Gilbert. *Semaine méd.*, Paris, 1900, xx, 186.

² Kirikoff. *St. Petersburg. med. Wchnschr.*, 1902, xxvii, 357.

³ Milian. *Progrès méd.*, April 14, 1900.

⁴ Schachmann. *Thèse de Paris*, 1889.

1/ size of the laser and spleen and in the degree of the

1/ Private may be troublesome, but is not constant.



quadrants, partly from the large size of the liver and spleen, and partly from tympanites and weakness of the abdominal walls. Until late in the disease ascites is absent or very slight, and is then due to intercurrent attacks of perihepatitis and perisplenitis. Towards the termination of the disease ascites may be considerable from the development of secondary portal cirrhosis and toxæmia.

There is a sense of weight in the right hypochondrium, and periodic attacks of pain with tenderness over the liver and spleen, which may even suggest biliary colic, occur. There may be little or no enlargement of the subcutaneous veins around the umbilicus, but it cannot be said that this feature of portal cirrhosis is completely absent in hypertrophic biliary cirrhosis. It may develop as the result of superadded portal cirrhosis in the later stages of the disease.

Physical Signs.—The *liver* is much and uniformly enlarged, and, as a rule, smooth and firm to the touch, but occasionally somewhat irregular from perihepatic adhesions. Its dulness often extends upwards to the fourth rib in the right nipple line, and downwards to the umbilicus or even lower, and as far as the crest of the ilium. The pressure of the enlarged organ pushes the costal arch out. On palpation there is slight general without any localised tenderness. The gall-bladder is not distended. The enlargement of the liver is, generally speaking, progressive; it may vary from time to time, and increase in size during the exacerbations. Late in the disease it sometimes diminishes in bulk from some degree of contraction of the fibrous tissue, probably of that constituting the multilobular cirrhosis.

The *spleen* is firm, smooth on the surface, but not so hard as in myeloid leukaemia. When attacks of inflammation of the capsule supervene, friction may be heard with the stethoscope, and in some instances a soft blowing murmur may be audible over the spleen. It is very considerably enlarged—much more so than in common cirrhosis. It is more marked in children, in accordance with the fact that its capsule is more distensible than in adults. The spleen may, indeed, be not only relatively but absolutely heavier than the liver. The splenic enlargement may precede any enlargement of the liver; Boix¹ and Popoff² insist that it always does. Lereboullet³ describes the following forms of the disease, based on the relative size of the spleen and liver: (i) The ordinary or hepatic type, in which the liver and spleen are both considerably enlarged, Hanot's disease. (ii) Hypersplenomegalic biliary cirrhosis, in which the splenic enlargement is the predominant feature, the spleen being actually larger than the liver. (iii) Microsplenic biliary cirrhosis, in which the enlargement of the liver is the predominating feature. The spleen may not be enlarged. (iv) Atrophic biliary cirrhosis, in which the liver is small and the spleen large.

¹ Boix. *Compt. rend. Soc. Biol.*, 1898, 1, 297.

² Popoff. *Leçons cliniques*, St. Petersburg, 1896. Quoted by Boix.

³ Lereboullet. *Les Maladies du foie et leur traitement*, p. 315, 1910, Paris, Baillière et fils.

Chauffard¹ insists on the time relations between the hepatic and splenic enlargement and divides the cases into three groups: (i) The spleen and liver are simultaneously and equally affected. (ii) The spleen is affected first and in a greater degree—metasplenomegalic hypertrophic biliary cirrhosis; the cirrhosis he believes to be secondary to poisons manufactured in the spleen. (iii) The liver enlarges first and probably determines the splenic enlargement—presplenomegalic hypertrophic biliary cirrhosis.

Jaundice is slight at first and becomes more marked as the disease progresses; it is permanent, but varies in degree, being intensified during the exacerbations. After these crises it recedes a little, but, on the whole, slowly progresses. The jaundice may eventually become very dark or green. There may be considerable brown discoloration of the skin, resembling that of Addison's disease. This melanoderma may occur early, before the onset of jaundice (Roger Smith), but usually it is combined with the icteric staining of the skin. There may be troublesome itching, and from scratching the skin may become covered by an eczematous or lichenous eruption. Long-continued jaundice may lead to xanthoma. I have seen it in a case in which moderate jaundice had existed for nine months. It is said that in some cases of otherwise typical hypertrophic biliary cirrhosis jaundice is absent.

Haemorrhages.—In the later stages there may be cutaneous petechiae, epistaxis, bleeding from the gums and throat, and in exceptional instances haemoptysis, haematuria, and haematemesis.

Physical Development.—The patients are thin, badly nourished, and, when not adults, frequently small for their age. As in other conditions, such as cretinism, hereditary syphilis, and congenital morbus cordis, growth and bodily development may be greatly interfered with and the onset of puberty and in girls menstruation postponed. To this condition the term "infantilism" is applied. The skin is dry. Oedema of the feet may occur in the late stages.

Clubbing of the Fingers.—Some cases of long standing shew clubbing of the terminal phalanges of the fingers and toes. The terminal phalanx may be expanded and broadened so that the digit resembles a spoon or even a pendulum. The nails may be overcurved and longitudinally striated; in extreme instances the nails have been compared to a parrot's beak. This change is the same as that in congenital morbus cordis and chronic lung disease, and is sometimes spoken of as "Hippocratic fingers." It is relatively common in biliary cirrhosis; Gilbert and Lereboullet² were able to refer to 40 cases in 1901. It is met with more often in children, in whom it was first described by Gilbert and Fournier,³ than in adults. Skiagraphy shews that there is no bony enlargement of the terminal phalanges (F. Taylor,⁴ Boutron⁵). The

¹ Chauffard. *Semaine méd.*, 1900, xx, 176.

² Gilbert et Lereboullet. *Gaz. hebdomadaire de méd.*, 1902, xlix, 1.

³ Gilbert et Fournier. *Rev. mens. des mal. de l'enf.*, Paris, 1895, xiii, 309.

⁴ Taylor, F. *Guy's Hosp. Rep.*, 1900, liv, 13.

⁵ Boutron. *Thèse de Paris*, 1899, No. 513.

1) and may ~~show~~ telangiectases.



clubbing is due to thickening of the soft tissues, and on the analogy of its occurrence in bronchiectasis and empyema the change is probably due to the action of toxins. But it is not associated with intra-thoracic disease, and there is no reason to think that it is due to embarrassment of the right lung by the upward pressure of the enlarged liver. Neither is it confined to this form of hepatic disease, for it was well marked in a boy aged seventeen, with syphilitic stricture of the bile-ducts (*vide* Fig. 49), and in very rare instances it has occurred in portal cirrhosis (p. 229). In a few cases of hypertrophic biliary cirrhosis bulbous fingers have been associated with perforating ulcer of the foot and neuritis.

Reference for the subject of clubbed fingers in biliary cirrhosis may also be made to Roger Smith, *Trans. Clin. Soc.*, 1898, xxxi, 258; Parmentier et Castaigne, *Sem. méd.*, 1901, xxi, 94; Rhorassandri, *Thèse de Paris*, 1900, No. 160; Ebstein, E., *Deutsches Arch. f. klin. Med.*, Leipz., 1906, lxxxix, 67.

Arthritis, Hypertrophic Osteo-Arthropathy, etc.—Enlargement of the ends of the bones, synovitis, and pain in the joints, so-called biliary rheumatism, has been described (Gilbert and Fournier).

Wynn¹ collected 11 cases of biliary cirrhosis with hypertrophic osteo-arthropathy. The change has been referred to toxic absorption from the alimentary canal. But against this view it must be borne in mind that gastrointestinal disturbance is much more constant in portal than in biliary cirrhosis, and that bulbous fingers are extremely rare and osteo-arthropathy almost unknown in portal cirrhosis (*vide* p. 230), which is a very common disease as compared with biliary cirrhosis.

In a man aged twenty-three years, who rapidly developed the clinical picture of hypertrophic biliary cirrhosis, the right shoulder, pelvis, and hip were depressed without any spinal curvature to account for it. The patient was unconscious of the condition and could by an effort temporarily correct it. Sicard and Remlinger² thought that the enlarged liver might possibly have some part in bringing about this curious attitude, though it had not been noticed in cases with much bigger livers.

Nervous System.—As a rule, there is nothing special to note with regard to the nervous system. As the result of jaundice there may be some mental depression and failure of memory, and occasionally emotional disturbance. Marked drowsiness is not very rare. In the terminal stages toxæmic symptoms, such as delirium, coma, and convulsions, appear. I have seen peripheral neuritis with numbness of the fingers, but this appears to be quite unusual.

The *heart* tends to dilate, and a systolic mitral murmur or hæmic murmurs may be heard at some time during the course of the disease. The *pulse* is regular, of fair tension, and not slow.

Blood.—There is usually a secondary anaemia, the red corpuseles being reduced to between 4,500,000 and 2,200,000, and the colour-index is below 1.

¹ Wynn, W. H. *Birmingham Med. Rev.*, 1904, iv, 283.

² Sicard et Remlinger. *Rev. de méd.*, Paris, 1897, xvii, 693.

Emerson¹ met with high counts—7,800,000 and 8,500,000—in 2 out of 5 cases; in one the count was as low as 1,504,000. Hayem and Cabot² found that in exceptional instances the amount of haemoglobin may be relatively excessive. Thus in Hayem's case there were 1,884,000 red corpuscles with 50 per cent of haemoglobin; the diagnosis was confirmed by a necropsy.

There is no poikilocytosis (Milian³); the blood is less coagulable than in health. Hanot stated that leucocytosis was present, but it appears that leucocytosis is not constant, and may be absent. When present, it is not high, varying between 9,000 and 15,000, and is due to an increase in the polymorphonuclears (Milian).

Hanot and Meunier⁴ found leucocytosis in 5 cases, Cabot in 4 out of 6 cases, and Da Costa⁵ in 2 out of 6. It was absent in cases reported by Taylor, and Milian and Kirikoff⁶ found that leucocytosis was only present when there were complications, and that a normal count or leucopenia was the rule. Bigart's⁷ observation of increase in the number of mast cells appears to be unique and may have been due to some independent factor.

Respiratory System.—There may be shortness of breath, due to the upward displacement of the diaphragm, anaemia, and cardiac dilatation. Occasionally, as part of the general haemorrhagic tendency, haemoptysis may occur. Cough is sometimes persistent, and suggests tuberculosis, but tubercle bacilli are very rarely found in the sputum.

Urine.—The quantity passed varies considerably; usually it is increased, but during the exacerbations it may be diminished. Milian⁸ lays stress on polyuria as a characteristic feature. It is high-coloured and rich in urinary pigments. Urobilin and indican are both occasionally present. Bile pigment is practically always present. Unlike the concentrated urine of portal cirrhosis, there is little tendency to deposit urates. There is usually no albuminuria; when present, it has been noticed to be intermittent. Casts, if carefully looked for, are nearly always found; their presence appears to depend on the jaundice. The amount of urea varies; it may be normal or at times be diminished. Glycosuria does not occur. As the liver cells preserve their nutrition for a considerable period, alimentary glycosuria, induced by giving three ounces of sugar on an empty stomach, cannot be produced in most cases.

The toxicity of the urine is said to be feeble, and this has been used as an argument against the view that hypertrophic biliary cirrhosis is primarily due to a general haemic infection. The freezing-point of the urine, or its cryoscopic value, has been found to be high (Ferrannini⁹).

¹ Emerson. *Clinical Diagnosis*, p. 587, 1906.

² Cabot. *Examination of the Blood*, p. 250.

³ Milian. *Bull. Soc. Anat.*, Paris, 1903, 6. s., v, 13.

⁴ Hanot et Meunier. *Compt. rend. Soc. Biol.*, Paris, 1895, xlvii. 49.

⁵ Da Costa. *Clinical Hematology*, p. 352, 1892.

⁶ Kirikoff, *Ztschr. f. klin. Med.*, 1898-99, xxxvi, 444; Kirikoff und Korobkoff. *Russ. Arch. f. Path., klin. Med., u. Bakt.*, St. Petersburg, 1902.

⁷ Bigart. *Compt. rend. Soc. Biol.*, 1902, liv, 1529.

⁸ Milian. *Bull. Soc. Anat.*, Paris, 1901, lxxiv, 323.

⁹ Ferrannini. *Zentralbl. f. inn. Med.*, 1903, xxiv, 273.





Termination.—In uncomplicated cases the disease slowly progresses until a fatal toxæmic condition results from destruction of the liver cells. The “typhoid” state develops and the patient becomes more jaundiced, drowsy, and passes into coma. During this stage ascites may appear, or in rare instances death may be precipitated by fatal gastro-intestinal hæmorrhage.

A married, childless woman, aged thirty-two, who had had one miscarriage, was admitted to St. George's Hospital with jaundice of four months' duration, a greatly enlarged and tender liver, enlarged spleen and no ascites, but a history of several attacks of hæmatemesis. The urine was bile-stained and contained a trace of albumin. There were no distended abdominal veins. There was a systolic murmur over the pulmonary artery. There was no definite history of alcoholism, but it was suspected. A few days after admission hæmatemesis recurred and was often repeated; the patient became delirious and finally comatose, and in spite of being bled from one arm to about a pint and transfused to two pints in the other arm, she died. At the autopsy there was no ascites. The liver, weight 7 pounds 9 ounces, was slightly irregular on the surface and on section shewed fine cirrhosis; it was deeply bile-stained. The bile-ducts were pervious and the gall-bladder contained dark bile but no calculi. Portal vein healthy. Microscopically, liver cells very fatty, no signs of acute atrophy, numerous so-called new bile-ducts. Cirrhosis, comparatively slight, was mainly unilobular.

Death may be due to some acute infection, such as pneumonia, erysipelas, or peritonitis. Erysipelas is very prone to attack patients with chronic jaundice, and, from their want of resistance, to prove fatal; but in hypertrophic biliary cirrhosis erysipelas, though a severe complication, is not necessarily fatal. If acute infection falls on the liver itself, the symptoms of icterus gravis result. Primary carcinoma in a liver shewing hypertrophic biliary cirrhosis has been recorded (Goldzieher and Bókay¹).

Diagnosis.—Chronic jaundice without complete biliary obstruction, as shewn by the colour of the faeces, the occurrence of periodic exacerbations, and considerable enlargement of the liver and spleen, without any evidence of cholelithiasis, especially in a young person, are the essential points on which to base a diagnosis of hypertrophic biliary cirrhosis.

Differential Diagnosis.—In cases of *portal cirrhosis* with big livers and intercurrent jaundice the diagnosis depends on the jaundice being transitory and not permanent, on the comparatively slight splenic enlargement, and on the history and presence of signs of common cirrhosis. It cannot, however, be maintained that the two diseases (portal and biliary cirrhosis) are always distinct, either anatomically or clinically. Sometimes they are combined, and not infrequently the two diseases overlap in the same way as the parenchymatous and interstitial forms of nephritis.

The following case presented features of both diseases, but it might

¹ Goldzieher und Bókay. *Virchows Arch.*, 1911, cciii. 75.

also be interpreted as a case of portal cirrhosis with acute and recent inflammation of the intrahepatic bile-ducts :

A man aged forty-seven died in St. George's Hospital ; he had had hæmatemesis and ascites which required tapping ; for the last three weeks of his life he was delirious and jaundiced. His liver weighed 50 ounces and was typically hobnailed ; microscopically it shewed multilobular and unilobular cirrhosis, a large number of pseudobile canaliculi, and microscopic calculi in the bile capillaries. The spleen weighed 18 ounces.

In *haemochromatosis* there is widespread pigmentation of the body with secondary cirrhosis of the liver and pancreas, the liver is enlarged and some of the symptoms resemble those of hypertrophic biliary cirrhosis. The skin, however, though pigmented, is seldom jaundiced, and in five-sixths of the cases there is glycosuria (bronzed diabetes).

In *obstructive jaundice* the liver may be enlarged and swollen from retained bile ; but this condition differs from hypertrophic biliary cirrhosis in the acholic faeces, the absence of splenic enlargement, and in many cases an enlarged gall-bladder can be made out.

Chronic jaundice due to a calculus in the common duct may imitate hypertrophic biliary cirrhosis in the periodic attacks of intermittent hepatic fever, and in the fact that the stools are not necessarily devoid of bile. Calculi usually occur later in life than biliary cirrhosis, the periodic attacks of pain are more severe than in hypertrophic biliary cirrhosis, and the spleen is not enlarged.

In *alveolar hydatid* jaundice and splenomegaly may occur, but the condition is excessively rare (*vide p. 425*).

In *ordinary hydatid disease* the spleen is not enlarged, the periodic attacks of fever and pain are absent, and jaundice when present is either due to rupture of a cyst into the duct, in which case there is usually continued fever, or due to pressure on the larger ducts with complete exclusion of bile from the intestines.

In *prolonged catarrhal jaundice* the spleen is either not enlarged or very slightly, and bile is absent from the faeces.

In *chronic splenomegalic hæmolytic jaundice* the liver is either not enlarged or only slightly and temporarily, the blood shews fragility of the red corpuscles, the urine is free from bile, and pruritus, xanthoma, and mal-development do not occur (*vide p. 537*).

In *Keil's disease* the clinical course is rapid and acute, whereas in *hypertrophic biliary cirrhosis* it is a matter of years, not of days.

Malaria can be eliminated by examination of the blood and by the failure of quinine to affect the disease.

Some rather exceptional cases of *syphilitic disease of the liver with chronic jaundice* and very considerable enlargement of the liver and spleen may imitate hypertrophic biliary cirrhosis. Syphilitic lesions elsewhere, a positive Wassermann reaction, albuminuria as pointing to lardaceous disease as the cause of splenic enlargement, irregularity of the surface of the liver from gummas, the presence of enlarged veins near the umbilicus,



and the beneficial effects of antisyphilitic treatment point to syphilis. In the case described on p. 380, the presence of gummas on the limbs pointed to syphilis, but in other respects the features resembled those of Gilbert and Fournier's splenomegalic type of hypertrophic biliary cirrhosis.

Tuberculosis implicating the Liver.—Géraudel¹ has collected a number of cases in which tuberculosis gave rise to hepatic and splenic enlargement and chronic jaundice.

Banti's Disease.—There is a gradual transition between (a) cases of so-called metasplenomegalic biliary cirrhosis, in which the splenic enlargement precedes any manifest change in the liver, and (b) cases of chronic splenic anaemia which eventually develop a terminal cirrhosis of the liver and jaundice—so-called Banti's disease. To distinguish between the two a reliable history is necessary. Chronic splenic anaemia presents anaemia of the chlorotic type, an absence of leucocytosis or even a diminished number of leucocytes (leucopenia), and recurrent gastrointestinal haemorrhages before the development of jaundice; whereas in metasplenomegalic biliary cirrhosis there would be practically an absence of symptoms during the period in which splenomegaly is the only physical sign.

Duration.—Though the disease must be regarded as incurable, it is essentially chronic, and jaundice may exist for ten years or even longer; Goluboff² speaks of twelve years' duration. The average duration is about five years. In a few instances the disease runs an acute course, and then proves fatal within two years.

The *prognosis* is bad; the disease is incurable, but its progress is often extremely slow, and patients may retain fair strength for years. The patient's environment influences the outlook; careful treatment and supervision may be followed by improvement. An easy life in a healthy locality will prolong life, whereas overwork, exposure to cold and wet, and insanitary conditions will surely lead to deterioration.

The patient's general nutrition has, of course, an important bearing on the prognosis. Wasting and the recurrence of exacerbations and of haemorrhages at shorter intervals shew that the disease is advancing towards its termination. The incidence of complications, such as pneumonia, peritonitis, or erysipelas, makes the outlook very serious. Erysipelas may be recovered from if the urinary excretion is well maintained. Clubbing of the fingers is only met with in long-standing cases, and is an indication that the course of the disease has been slow.

The general lines of *treatment* are much the same as in portal cirrhosis. In certain points there are differences: thus, a more generous diet may be allowed than in portal cirrhosis, while itching of the skin due to jaundice is more, and ascites and haematemesis less, likely to require treatment than in ordinary cirrhosis. In the early stages an attempt

¹ Géraudel. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1909, xxvi. 24.

² Goluboff. *Ztschr. f. klin. Med.*, Berl., 1894, xxiv. 353.

may be made to put the patient in more healthy surroundings and to remove him from the conditions, among which the water-supply may play a part, that favoured the onset of the disease. Fresh air is important, but exposure to chills, and especially to cold and damp weather, should be avoided, and the patient should be warmly clad. A course at Homburg, Ems, Neuenahr, Kissingen, Vichy, Vals, Harrogate, may be tried. If the patient goes to Carlsbad, the course must be comparatively mild.

The *diet* should be simple and nourishing; irritating and unduly stimulating articles of food should be carefully excluded. Milk should be given freely, eggs, bread and butter, simple puddings, fish, and occasionally meat may all be taken. Alcohol should be avoided; or if taken at all, in small quantities and well diluted. Water should be drunk freely, but it will be advisable to have it boiled when the patient is still living in the house where the disease developed.

Intestinal fermentation and putrefaction should be prevented by careful dieting, correction of constipation, and by minute doses of calomel ($\frac{1}{40}$ — $\frac{1}{20}$ of a grain) three times a day; rather larger doses ($\frac{1}{6}$ — $\frac{1}{2}$ grain) may be employed in single doses to combine its antiseptic and purgative properties. Calomel is preferable to salol, β -naphthol, betol, and the synthetic intestinal antiseptics. Saline purgatives, such as sulphate of magnesium and sulphate of sodium in combination, are also useful in preventing intestinal fermentation, while mineral waters may be employed with the same object. The catarrhal condition of the small bile-ducts should be treated by drugs which, when excreted into the intrahepatic ducts, disinfect the ducts; for this purpose urotropin in combination with salicylate of sodium should be given.

Itching of the skin may be treated externally by warm baths or fomentations with carbolic acid lotion; internally lactate of calcium in 20-gr. doses or antipyrin, grs. v.—x., may be employed. Small hypodermic injections of pilocarpine have also been recommended (*vide* p. 567).

Surgical Treatment.—Terrier¹ and Delagénère² drained the gall-bladder in some cases with good results. Thus, in 13 cases tabulated by Maurice Guillot³ 10 were cured; Greenough⁴ adds 4 cases, making up a total of 17 cases, of which 13 were relieved. It is not certain that all the cases were of the same type; some of them may possibly have been examples of chronic infective cholecystitis and cholangitis and not of genuine biliary cirrhosis (*vide* Michaux⁵). The drainage of the gall-bladder was continued for periods varying from ten days to three months, and in some instances the bile, which was at first infected, became aseptic.

¹ Terrier. *Rev. de chir.*, Paris, 1892, xii, 553.

² Delagénère. *Arch. prov. de chir.*, Paris, 1897, vi, 310.

³ Guillot, M. *Gaz. hebdom. de méd.*, Paris, 1902, N.S., vii, 49.

⁴ Greenough. *Am. Journ. Med. Sc.*, 1902, cxxiv, 979.

⁵ Michaux. *Rev. de chir.*, Paris, 1901, xxiii, 126.

Con. Tréville, Es. an. Martigny, Vittel.



OBSTRUCTIVE BILIARY CIRRHOSIS

By obstructive biliary cirrhosis is meant a fibrosis spreading from the bile-ducts around the lobules of the liver and due to obstruction of the large bile-ducts.

History.—The conception of cirrhosis due to biliary obstruction was first prominently brought forward by Charcot and Gombault¹ in 1876, though three years previously Wickham Legg² in England had described a clinical case with full pathological details. In 1882 Mangelsdorf³ collected 184 cases, and in 1901 W. W. Ford⁴ and in 1903 Weber⁵ argued in favour of this sequence of pathological events.

Experimental Ligature of the Bile-ducts.—As bearing on the production of obstructive biliary cirrhosis, numerous experiments have been performed in which the bile-ducts have been ligatured and the liver subsequently examined for any fibrosis. The conclusions thus arrived at are by no means uniform.

Mayer⁶ in 1872 ligatured the common bile-duct of cats and produced dilatation of the bile-ducts with intralobular and extralobular fibrosis. Charcot and Gombault's⁷ (1876) results, like the earlier experiments of Wickham Legg⁸ (1873), shewed that ligature of the duct led to dilatation of the intrahepatic ducts with fibrosis around the individual hepatic lobules (insular cirrhosis) and into their substance (intralobular cirrhosis). The lobules tended to undergo atrophy, while numerous newly formed bile-ducts in the perilobular tissue passed by a gradual transition into the liver cells at the margin of the lobule. Somewhat similar results were obtained by Chambard, and by Foa and Salvioli. Charcot and Gombault referred these changes to the irritating properties of the retained bile, and incidentally mentioned that the bile contained "vibrios." Maffucci⁹ also induced cirrhosis by ligaturing the bile-duct.

As these results were obtained before the days of antiseptics, it has often been urged that the cirrhosis was due, not to mechanical pressure and irritation exerted by the retained bile, but to infection. Thus, Steinhaus¹⁰ found that after ligature of the bile-ducts in guinea-pigs, who were killed at periods varying from six hours to ten days, no interstitial hepatitis was produced unless infection occurred. The interval of ten days is very short, but ~~as~~ most of the animals died within a fortnight after ligature of the common duct, ~~this was~~ ~~unavoidable~~. In order to keep animals alive longer Josselin de Jong¹¹ ligatured individual branches of the hepatic duct instead of the common bile-duct and obtained much the same results as Steinhaus. Similar experiments in the

¹ Charcot et Gombault. *Arch. de physiol. norm. et path.*, 1876, 2. s., iii, 272.

² Legg, Wickham. *St. Barth. Hosp. Rep.*, 1873, ix, 161.

³ Mangelsdorf. *Deutsch. Arch. f. klin. Med.*, 1882, xxxi, 522.

⁴ Ford, W. W. *Am. Journ. Med. Sc.*, 1901, cxxi, 60.

⁵ Weber, F. P. *Trans. Path. Soc.*, 1903, liv, 103.

⁶ Mayer. *Med. Jahrb.*, Wien, 1872, ii, 133.

⁷ Charcot et Gombault. *Arch. de physiol. norm. et path.*, Paris, 1876, 2. s., iii, 272.

⁸ Legg, W. *St. Barth. Hosp. Rep.*, 1873, ix, 161.

⁹ Maffucci. *Gior. internaz. delle sc. med.*, 1882, N.S., iv, 889.

¹⁰ Steinhaus. *Arch. f. exper. Path. u. Pharm.*, 1891, xxviii, 432.

¹¹ Josselin de Jong. *Inaug. Diss.*, Leyden, 1894. Quoted by Harley and Barratt.

hands of Nasse,¹ and of Vaughan Harley and Barratt,² shewed that intralobular fibrosis resulted. The latter observers ligatured the left hepatic duct in cats and kept them alive for four to sixteen months, and in dogs without any jaundice resulting; microscopic sections of the left and of the healthy right lobe could then be compared. The changes observed were not absolutely constant, but in many instances well-marked interlobular fibrosis, hyperplasia of the interlobular bile-ducts, and atrophy of the hepatic lobules, beginning at the periphery, were present in the area of the liver corresponding to the ligatured bile-duct. Ligature of the common duct in frogs, guinea-pigs, and rabbits under antiseptic precautions gave rise to some fibrosis (Lahousse,³ Beloussow,⁴ Gerhardt⁵).

~~There is thus considerable difference of opinion whether or not fibrosis is produced. In some cases in which the ligature is applied to the duct near the duodenum the part of the duct above the ligature may contain micro-organisms, so that although the ligature itself is aseptic, the conditions are complicated. Lamacq⁶ points out that in dogs the liver may normally contain infective nodules. His results shew that when infection is avoided, ligature leads to necrosis of the liver cells in rabbits when the bile pressure is relatively high, but that in dogs necrosis is rare and when present not marked, and that~~ No leucocytic infiltration or fibrosis occurred around the areas of necrosis and no proliferation of bile-ducts. The same results were obtained by Ribadeau-Dumas and Lecène⁷ in guinea-pigs. By aseptic ligature of the common bile-duct M. Richardson⁸ produced cirrhosis in rabbits, and Milne⁹ in cats.

To sum up the effects of ligature of the bile-ducts: fibrosis may be absent, it may be present and be due to infection, or may, even where infection is absent, be found in varying degrees. This fibrosis following aseptic ligature may be explained in several ways: it may be regarded merely as a fibrous replacement, perhaps more apparent than real. In cases such as Nasse's and Harley's and Barratt's, in which one hepatic duct is ligatured and the fibrosis is limited to the corresponding part of the liver, this may be the explanation. Harley and Barratt, however, referred the fibrosis to the continued slight irritation of the bile. In other instances the cirrhosis may be due to toxic influences which are brought into existence by failure of the liver properly to perform its antitoxic function of stopping and destroying poisons brought to it by the blood, especially that of the portal vein; in such an event the poisons would reach the liver a second time by the hepatic artery. Or, again, when the common bile-duct is tied the cirrhosis may be due to poisons absorbed from the alimentary canal, where, as the result of interference with the flow of bile, fermentation and putrefaction have

¹ Nasse. *Arch. f. klin. Chir.*, 1894, xlviii, 885.

² Harley and Barratt. *Journ. Path. and Bacteriol.*, 1901, vii, 203.

³ Lahousse. *Arch. de biol.*, Paris, 1887, vii, 187.

⁴ Beloussow. *Arch. f. exper. Path. u. Pharmac.*, 1881, xiv, 211.

⁵ Gerhardt. *Ibid.*, 1892, xxx, 1.

⁶ Lamacq. *Arch. de méd. expér. et d'anat. path.*, Paris, 1897, ix, 1135.

⁷ Ribadeau-Dumas et Lecène. *Ibid.*, 1904, xvi, 191.

⁸ Richardson, M. *Journ. Exper. Med.*, N.Y., 1911, xiv, 401.

⁹ Milne. *Quart. Journ. Med.*, Oxford, 1911-12, v, 415.

From many experiments ^{on rabbits} Roux and Larimore ^{x had} believe that biliary obstruction involving the intralobular bile canaliculi leads to a diffuse intralobular cirrhosis, that obstruction of the small bile ducts in the portal spaces sets up a pure unilobular cirrhosis and that obstruction of the large bile ducts is followed by a stellate fibrosis around them. Thus the diversity of the hepatic changes is due to differences in the duct levels at which the injurious factor is active. These experiments ^{results} carry conviction.

Roux, P. and L. D. Larimore J. exper. Med., Baltimore, 1920, XXII, 249

Experimentally Marshall Funkhley found that hypodermic injection and oral administration of salts of manganese produced a monobulbar atrophy with proliferation of the epithelium of the bile ducts and jaundice.

been excessive. Lastly, the fibrosis may be entirely independent of ligation of the bile-ducts and due to extrinsic causes developing after the duct has been ligatured.

Incidence.—The statistics of Mangelsdorf¹ shewed that up to 1882 the published cases of cirrhosis which could be ascribed to biliary obstruction numbered 184; between 1882 and 1900 W. W. Ford² collected 21 more and added 3 fresh examples. From his 21 cases collected from literature 10 may be deducted, since 9 belong to the group of congenital obliteration of the ducts and one was an example of congenital cystic disease of the liver. Cases of cirrhosis due to biliary obstruction are therefore not often described. The general opinion is that mechanical biliary obstruction seldom or never causes genuine

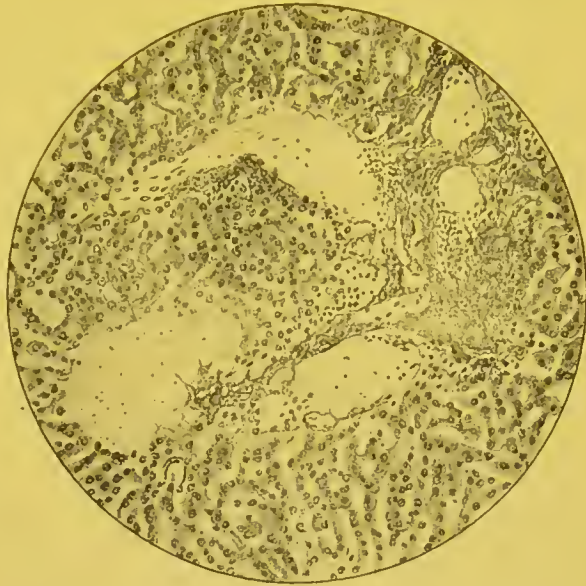


FIG. 40. — Focal necrosis due to biliary obstruction. From a guinea-pig whose bile-duct was compressed by a cyst. The pale areas shew complete necrosis of the liver cells; there is some small-celled infiltration around the portal space. The bile-ducts contained inspissated bile. (From a specimen kindly lent by Dr. J. H. Drysdale.)

cirrhosis, and that although fibrosis may be detected on microscopic examination, it is not of any clinical or practical significance.

The effects of biliary obstruction on the human liver, like those obtained by experimental work on animals, are not uniform, but there is very little evidence that biliary obstruction *per se* causes cirrhosis. When the common bile-duct is completely occluded from without, for example, by malignant disease of the head of the pancreas, there is dilatation of the ducts, but as a rule little or no fibrosis, while the liver cells are degenerated, atrophied, and occupied by bile pigment. The liver substance is atrophied and the organ is in a condition comparable to that of hydronephrosis. It is somewhat strange that manifest microbial infection does not occur more often, since the biliary stagnation must dispose to infection by micro-organisms reaching the liver by the bloodstream.

Malignant disease of the pancreas with complete biliary obstruction is not rare, but it is remarkable that it is hardly ever associated with cirrhosis of the liver. If biliary obstruction *per se* produced fibrosis of

¹ Mangelsdorf. *Deutsch. Arch. f. klin. Med.*, 1882, xxxi, 522.

² Ford, W. W. *Am. Journ. Med. Sc.*, 1901, cxxi, 60.

the liver, the association should be often seen. The cases are so few that it seems possible that when hepatic cirrhosis and malignant disease of the pancreas are found in the same person, the cirrhosis was the older lesion and was latent, and that the growth in the pancreas developed subsequently. Maffucci¹ and Legrand² have recorded cases in which these two conditions were associated.

In addition to the possibility that bacterial infection of the dilated bile-ducts, when obstructed by the pressure of a tumour from without, may occur from the blood-stream, it must be remembered that as complete obstruction entails absence of bile from the intestine, putrefactive and fermentative processes in the bowel become excessive and might lead to the production of poisons, which, when carried to the liver, would set up the ordinary portal or multilobular cirrhosis. This change would, indeed, in all probability be met with more often, were it not that the liver, being flooded with bile which has acquired toxic properties, as shewn by the focal necroses of the liver cells, is incapable of such reaction.

The cirrhosis of the liver found in association with congenital obliteration of the bile-ducts has been regarded by Thomson, Beneke, Ford, and Lavenson as secondary to the biliary obstruction and as a good example of obstructive biliary cirrhosis. It is, however, quite as reasonable to believe that the process starts in the smaller ducts, where it sets up pericholangitic fibrosis and then spreads to the larger ducts and gall-bladder, where it sets up obliterative cholangitis and cholecystitis (*vide* p. 651).

On the other hand, when a gall-stone is lodged in the common bile-duct, the results are not so constant; sometimes the changes are the same as in aseptic closure of the common duct, but other cases shew cholangitis and pericholangitis, which, if the process is chronic, result in fibrosis around the ducts. There seems to be very little doubt that the factor which determines fibrosis around the intrahepatic ducts in gall-stone obstruction is infection. As the result of prolonged biliary stasis, icteric necrosis of the liver cells occurs and fibrosis of a diffuse character may thus be favoured.

Mangelsdorf tabulated 54 cases of hepatic cirrhosis associated with gall-stones, in 16 of which calculi were found in the ducts. Parkes Weber³ collected 12 cases of biliary cirrhosis from obstruction of the larger ducts by gall-stones.

Hypertrophic biliary cirrhosis has been associated with gall-stones,⁴ but it is rare, as Naunyn⁵ has never seen it; the gall-stones in such cases must be regarded as secondary to, and not the cause of, the biliary cirrhosis.

¹ Maffucci. Quoted by Ford, *Am. Journ. Med. Sc.*, 1901, cxxi, 60.

² Legrand. *Rev. de méd.*, Paris, 1889, ix, 165.

³ Weber, F. P. *Trans. Path. Soc.*, Lond., 1903, liv, 105.

⁴ Compare Sharkey. *St. Thomas's Hosp. Rep.*, 1888, xviii, 245.

⁵ Naunyn. *Cholelithiasis*, p. 163, Transl. New Sydenham Soc., 1896.



When the gall bladder is able
 to concentrate the bile, as in
 complete obstruction of the common
 bile duct, the bile is thick &
 dark; when the obstruction is
 in the hepatic ducts, the bile
 is white and the condition of
 the liver has been called
 hydrops hepaticus (Rous,
 in: Medicine, Ross & Brown)

Morbid Anatomy.—*The liver* in mechanical obstruction of the bile-ducts, though enlarged in the early stages, is small at the necropsy, unless occupied by secondary growths or by a hydatid cyst. Its surface is irregular, shews dilated and varicose bile-ducts ~~filled with mucus~~, and is of a dark green colour. The dilatation of the ducts is not always uniform; it may indeed be localised, often near the margin of the left lobe.

In a case examined in St. George's Hospital there was an area, the size of the palm of one's hand and roughly divided into two by the falciform ligament, on the convexity of the liver, which was entirely composed of dilated bile-ducts.

Occasionally there are perihepatic adhesions. On section of the organ the dilated ducts are prominent and give the liver a sponge-like or honeycombed appearance; it is usually somewhat flabby from atrophy of the secreting cells, and cuts very differently from an ordinary cirrhotic liver. The liver parenchyma around the dilated bile-ducts shews atrophy, condensation, and some pericholangitic fibrosis. When acute infection has been superadded, there may be suppuration in or around the bile-ducts, and minute abscesses. The naked-eye appearances are therefore very different from those of hypertrophic biliary cirrhosis.

Further, the histological changes are not the same as those of hypertrophic biliary cirrhosis. In calculous obstruction the ducts are dilated and tend to become progressively more so in proportion to the duration of the obstruction, whereas in hypertrophic cirrhosis this does not occur. In biliary obstruction the larger ducts are chiefly affected and may shew cholangitis and pericholangitis, whereas in hypertrophic biliary cirrhosis the smallest intrahepatic ducts are inflamed. Degeneration of the liver cells and focal necroses are prominent in mechanical obstruction of the larger ducts, whereas in hypertrophic biliary cirrhosis the liver cells maintain their nutrition for long periods.

The changes consist in dilatation of the bile capillaries around the intralobular veins, rupture of them, and escape of bile into the lymph spaces between the sinusoids and the liver cells (Mallory¹). The liver cells shew degeneration and infiltration with bile pigment (Carnot and Harvier²). The columns of small cubical cells, known as "pseudobile canaliculi," are described in many cases, but are certainly not always present. When fibrosis occurs it spreads out from the larger bile-ducts and may give rise to multilobular cirrhosis or to a more diffuse form of cirrhosis which not only tends to surround the individual lobules, but invades their substances and passes between the hepatic cells. From his study of 184 cases of cirrhosis, thought to be due to biliary obstruction, Mangelsdorf concluded that no particular form of cirrhosis could be said to depend on biliary obstruction.

The spleen is sometimes small or of normal size, but in cases in which

¹ Mallory. *Johns Hopkins Hosp. Bull.*, Balt., 1911, xxii, 70.

² Carnot et Harvier. *Arch. de méd. expér. et d'anat. path.*, Paris, 1907, xix, 76.

considerable fibrosis of the liver coexists with obstruction of the larger ducts, as in Weber's cases, there may be enlargement, though not to the same degree as in hypertrophic biliary cirrhosis.

The pancreas in cases in which a calculus occupies the lower end of the bile-duct or the ampulla of Vater may, from obstruction combined with infection of its duct, shew dilatation of the duct and fibrosis with atrophy of the secreting tissue of the organ. This chronic interstitial pancreatitis is perilobular and somewhat coarse; only in very late stages does it become interacinous; as a rule diabetes mellitus is not produced.

Clinical Features.—When cirrhosis of the liver, whether pericholangitic or portal, occurs in a patient with biliary obstruction, it does not, as a rule, reveal itself by any special signs or symptoms, the features being those of biliary obstruction (*vide* p. 540). Complete aseptic obstruction of the common bile-duct leads to dilatation of the intrahepatic ducts and to focal necrosis of the liver cells. The functional activity of the liver is thus very gravely interfered with and, as a result of this hepatic inadequacy, cholaemia or biliary toxæmia results, a condition which is more rapidly fatal than cirrhosis. The symptoms are those of complete obstructive jaundice and cholaemia; the gall-bladder is usually dilated; this and the history should distinguish it from impacted gall-stone.

Cases of long-standing gall-stone obstruction of the common bile-duct associated with ordinary portal cirrhosis undoubtedly occur. As a rule, symptoms of portal cirrhosis are absent or cast into the shade by those of biliary obstruction. When the clinical features of ordinary portal cirrhosis follow obstruction, due to gall-stones or other causes, the cirrhosis is reasonably explained as the result of poisons manufactured in the intestines and carried to the liver by the portal vein.

Ford collected 10 cases in which ascites and other symptoms of portal cirrhosis were associated with obstruction of the common bile-duct. In 6 of these the obstruction was by gall-stones, and in 4 by tumours, glands, or a cicatrix pressing on the duct from without.

In instances in which a gall-stone passes into the common bile-duct without any history of colic diagnosis may be difficult. As time progresses, bile may escape by the side of the stone into the duodenum and the faeces are no longer pale; they then contain stercobilin, just as in hypertrophic biliary cirrhosis. In differentiating these two conditions, the size of the spleen is important; it is much enlarged in hypertrophic biliary cirrhosis, whereas in gall-stone obstruction splenomegaly, if present, is relatively insignificant. In hypertrophic biliary cirrhosis the liver is greatly increased in size; in biliary obstruction it may be swollen from retention of bile, but in the late stages it becomes smaller.

The **treatment** is that of obstructive jaundice by operative measures and by symptomatic remedies (*vide* p. 566). In the rare cases with ascites and symptoms pointing to ordinary cirrhosis the treatment should be on the lines of that disease.



HEPATIC CIRRHOSIS IN CHILDREN

CIRRHOSIS in children is probably not so rare as might be concluded from C. West's¹ experience of only 4 examples among 70,000 cases of children's diseases. In fact, at the Hospital for Sick Children, with which West was connected, there were in forty-five years 40 cases of cirrhosis among 5500 necropsies, or 73 per cent (Forbes²). In 17,891 necropsies in children there were 33 cases of cirrhosis, or 18 per cent (Jones³). In 1889 Hatfield⁴ was able to refer to 156 examples, including Palmer Howard's⁵ 63 cases, of cirrhosis in children. In 1906 Jones collected from the European and American literature of fifty years, 300 cases of various forms of cirrhosis. Musser's⁶ 529 cases included Ghose's 400 cases of biliary cirrhosis in infants in India, a special and common disease in Calcutta, but on a somewhat different footing from the sporadic cases seen in temperate climates (*vide* p. 335). Children are affected by the forms of cirrhosis seen in adults, and in the main react in very much the same manner. The following summary will be confined to points deserving special attention.

The various forms of cirrhosis of the liver seen in children may attack more than one member of the family; this depends on hereditary factors, of which syphilis is pre-eminent, and on influences favouring cirrhosis, such as alcohol and improper food, which form part of the family environment.

The *unicellular cirrhosis of hereditary syphilis* and the lesions of delayed hereditary syphilis are dealt with elsewhere (p. 370); after recovery from unicellular cirrhosis the liver is probably left with its resistance so diminished that it may readily become affected by ordinary portal cirrhosis, the resulting change being neither due to syphilis nor curable by antisypilitic treatment, but disposed to by the influence of former syphilis, and therefore parasypilitic and comparable to tabes dorsalis and general paralysis of the insane. Some cases of portal cirrhosis in early life may thus be related to syphilis (*cf.* Payne⁷).

There are other forms of intra-uterine or *congenital cirrhosis*. It occurs in congenital obliteration of the bile-ducts, and in cases which clinically resemble that group, but anatomically do not present obliteration of the ducts. It is reasonable to believe that the change is due to poisons conveyed from the mother to the fetus (*vide* p. 651).

Vanverts and Ramond⁸ record a case of congenital ascites and hepatic cirrhosis in which the fetus' abdomen had to be tapped before it could be

¹ West, C. *Lectures on Diseases of Infancy and Childhood*, p. 654, 1884.

² Forbes. *Trans. Path. Soc.*, Lond., 1906, lvii, 354.

³ Jones. *Brit. Journ. Child. Dis.*, 1907, iv, 1.

⁴ Hatfield. *Cyclopaedia of Children's Diseases*, 1889, iii, 488.

⁵ Palmer Howard. *Am. Journ. Med. Sc.*, Phila., 1887, xciv, 350.

⁶ Musser, J. H. *Supplement to Cyclopaedia of Children's Diseases*, p. 798, 1899.

⁷ Payne. *Trans. Path. Soc.*, Lond., 1900, li, 366.

⁸ Vanverts et Ramond. *Bull. Soc. Anat.*, Paris, 1896, lxxi, 153.

delivered. The liver was enlarged and cirrhotic. There was no evidence of syphilis, alcoholism, or tuberculosis in the parents.

Portal cirrhosis is rare; among ^{16,123} 12,461 necropsies, during the ⁵² ~~last~~ years 1866–1905 at St. George's Hospital, there were only 8 cases under twenty-one years. In Woolley's¹ 90 collected cases under twenty-one years of age there were 48 males and 42 females, the average age was eleven years, and was practically the same in the two sexes; 70, or 77·8 per cent, occurred between the ages of six and fifteen years. As in adults, the liver may be larger than normal, or may be small and markedly hobnailed. In cases with pronounced nodular hyperplasia the liver may look as if occupied by multiple new-growth. In some cases the cirrhosis can be traced to precocious alcoholism, or to some specially irritating kind of food, such as fish soaked in vinegar. It is, therefore, not surprising that occasionally two or more children in the same family suffer from portal cirrhosis (*vide* p. 180). Jones has collected 74 cases of alcoholic cirrhosis in children. In many cases alcoholism can be excluded and some other cause must be sought for, such as gastro-enteritis or the specific fevers. Probably some ~~of the~~ cirrhotic livers ^{of} early life are, like granular kidneys in childhood, in reality parasymphilitic (*vide* p. 381). On the other hand, portal cirrhosis is not, like chronic interstitial nephritis and interstitial keratitis (Nettleship²), commoner in female than in male children.

Clinical Features.—Haematemesis seems less frequent than in adults, possibly because the spleen is more distensible and therefore accommodates relatively more portal blood than in the adult. Saunal,³ however, recorded fatal haemorrhage from an oesophageal varix in a girl aged twelve years (*vide* p. 266). Haemorrhages elsewhere, from the nose and into the skin, and depending on severe toxæmia, are quite as frequent as in adults. Spider-like angiomas on the skin of the face are not so often seen in children as in adults. Enlargement of the liver and spleen is more prominent than in adults. This may in part depend on the liver being relatively larger in children and on greater power of repair and hyperplasia of the liver in early life. The spleen is more readily distended in early life. In children cases of mixed portal and biliary cirrhosis are not infrequent; this, again, bears on the more marked enlargement of the liver and spleen. A

Fever is more frequent in children than in adults, and may be so marked as to suggest enteric fever or generalised tuberculosis.

In a case of Wickham Legg's⁴ a boy aged twelve years was first thought to have enteric fever and later acute tuberculosis. Another case regarded as enteric fever occurred at St. George's Hospital (*vide* p. 220).

Ascites is common, and is very likely to be regarded as evidence of tuberculous peritonitis. In Woolley's 90 cases there was ascites in 59,

¹ Woolley. Unpublished Thesis for M.D. Cantab., 1906.

² Nettleship. *Roy. London Ophthalmic Hosp. Rep.*, 1904–6, xvi, 1.

³ Saunal. *Thèse de Paris*, 1892.

⁴ Legg, Wickham. *St. Barth. Hosp. Rep.*, 1877, xiii, 148.

^ Subacute neurosis,

^ Exacerbations with increased abdominal distension, ~~and~~ hemorrhages, and fever occur.

The duration is
shorter, and 1

Patterson and Carmichael
described a form of familial
Cerebral degeneration chiefly
affecting the lenticular nuclei;
a mother, never jaundiced, though
was low spirited during her 12 pregnancies;
all the infants were slightly jaundiced
after birth, but the livers were normal.

~~Cases have also been reported~~
~~by L'hermite, Yokoyama and~~
~~Fischer~~ In 1919 Howard and
Royce collected 26 fresh cases, 13
reported by American neurologists, since
1912, and in 1921 Hall, who
proposed the name, hepato-lenticular
degeneration brought the total up to 66.

In 6 out of 30 cases examined after
death there was pigmentation of
Descemet's membrane of the cornea.

which was previously
thought to differentiate
pseudosclerosis from
Wilson's disease. Progressive
lenticular degeneration and
pseudosclerosis are different
manifestations of the same
disease (Greenfield, Paynton
and Waloke). It may be
mentioned that chronic
manganese poisoning produces
some of the symptoms of
paralysis agitans and
biliary cirrhosis.

Byrom Bramwell suggests
that some familial cases of
hepatic cirrhosis without nervous
symptoms are incomplete
cases of Wilson's disease.

~~L'hermite. Semaine Méd., Paris, 1912, xxvii, 121.~~

Howard, C.P. and Royce, C.E. Arch. Int. Med., Chicago, 1919, xxiv, 497
Hall, H.C. La dégénération hépato-lenticulaire, Paris, 1921

Yokoyama and Fischer. Virchow's Arch., 1913, cxi, 365.
Greenfield, Paynton, and Waloke. Quart. Journ. Med., Oxford, 1923-4, xvi, 385
Bramwell, B. Edin. Med. Journ., 1916
Patterson, D. and Carmichael, A.E. Brain, 1924, xlvii, 207

in 12 tuberculous peritonitis was diagnosed. Pulmonary tuberculosis is a very rare complication, but infection of the peritoneum may occur. In some cases a terminal suppurative peritonitis is met with. A curious symptom sometimes observed is ravenous appetite. Marked jaundice is rare; diarrhoea is more often associated with cirrhosis in children than in adults. The prognosis is probably worse than in adults.

In an interesting group of cases described by Ormerod,¹ Homén,² Gowers, and S. A. K. Wilson,³ the symptoms are nervous, and cirrhosis is entirely latent. Gowers⁴ described them as "tetanoid chorea," Anton⁵ as "dementia choreo-asthenica," and S. A. K. Wilson⁶ as "progressive lenticular degeneration." The disease is familial but not hereditary. The clinical features are bilateral tremor and spasticity, and in the late stages contractures. There is dysphagia and anarthria; but no real paralysis. There is symmetrical degeneration of the lenticular nucleus and multilobular and unilobular cirrhosis of the liver. Homén considered that the disease was the result of congenital syphilis. Wilson, who has collected 11 cases, excludes alcohol and congenital syphilis as causes, and believes that a toxin, probably not microbic and possibly a lipoid, exerts a selective action on the lenticular nuclei, comparable to the selective bile-staining of the lenticular nucleus in "Kernicterus" (*vide p. 509*).⁷

1) who collected 11 cases

and often enlargement of the spleen and Fick's

1) manufactured or in case

Hypertrophic biliary cirrhosis is relatively a commoner form of cirrhosis in children than in adults; it presents some special features which Gilbert and Fournier⁶ described as the juvenile type of the disease. Development is arrested and "infantilism" results. The cases may run an extremely protracted course, and the type of the disease may change, and eventually present the features of ordinary or portal cirrhosis (*vide p. 314*). For the account of the disease *vide p. 309*.

Cirrhosis in Young Children in India.—A peculiar form of cirrhosis among young native children in India, attacking chiefly Hindus, has been described by Gibbons,⁷ Ghose,⁸ and others.⁹ It occurs especially in, but is not confined to, Calcutta. It is common—Ghose has seen as many as 400 cases—and extremely fatal, often killing off one child after another in the same family; about 95 per cent of those attacked die from the disease before the end of the second year of life. In 1891–93 it caused 1748, and in 1907, 636 (Pearse) deaths in Calcutta; only six of Ghose's 400 cases recovered. It is not due to syphilis, alcohol, or malaria. It has been thought to depend on irritating bodies in the food, especially as the

¹ Ormerod, J. A. *St. Barth. Hosp. Rep.*, 1890, xxvi, 57.

² Homén. *Neurol. Centralbl.*, 1890, ix, 514.

³ Wilson, S. A. K. *Brain*, Lond., 1912, xxxiv, 295.

⁴ Gowers. *Diseases of Nervous System*, 1886, ii, 656; *Rev. Neurol. and Psychiat.*, Edin., 1906, iv, 249.

⁵ Anton. *München. med. Wchsehr.*, 1908, lv, 2369.

⁶ Gilbert et Fournier. *Compt. rend. Soc. Biol.*, Paris, 1895, xlvii, 419.

⁷ Gibbons, J. B. *Scientific Memoirs by Medical Officers of the Army of India*, 1891, part vi; and the *Ind. Lancet*, 1896, vii, 426.

⁸ Ghose. *Lancet*, Lond., 1895, i, 321.

⁹ Nil Ratan Sircar, *Ind. Lancet*, 1896, viii, 3; Mackenzie, *Lancet*, Lond., 1895, i; Pearse, *ibid.*, 1909, i, 265.

nursing mothers restrict themselves to a dry diet, and take a decoction of black pepper. It has been suggested that it may be due to kala azar (Castellani and Chalmers¹). The change begins as a unicellular cirrhosis, and then becomes interlobular; the amount of fibrous tissue may be very large, there is great destruction of the liver cells, and extensive formation of new bile-ducts. Kundrat and Paltauf of Vienna, to whom Gibbons shewed his specimens, regarded the change as an undescribed form of biliary cirrhosis. The spleen is usually enlarged. The disease is not congenital, but generally begins about seven months of age with fever and enlargement of the liver and spleen. Constipation, nausea, and jaundice, which eventually becomes intense, occur, and a terminal ascites may develop.

In rickets the liver is enlarged, in addition to being somewhat displaced downwards by deformity of the chest. As the result of absorption of toxic products from the alimentary canal there is some fatty change in the liver cells and fibrous hyperplasia in the portal spaces.² Hogben³ seems alone in describing the change as a biliary cirrhosis. The change seems to be temporary and does not appear to be the precursor or first stage of cirrhosis. The changes in the liver secondary to morbus cordis and spoken of as cardiac cirrhosis, pericarditic hepatic pseudo-cirrhosis, and cardio-tuberculous cirrhosis (*vide* p. 101) are chiefly met with in children.

TUBERCULOSIS OF THE LIVER AND BILE-DUCTS

SYNOPSIS

Introduction.

Paths by which tubercle bacilli reach the liver.

By the umbilical vein (congenital tuberculosis); hepatic artery; portal vein; lymphatics; bile-duct.

Forms of hepatic tuberculosis.

(I) Miliary tuberculosis.

(II) Local tuberculosis.

(a) Involving the bile-ducts.

(b) Caseous tuberculous masses.

(c) Tuberculous abscess.

Other changes in the liver associated with tuberculosis.

Focal necrosis. Fatty, lardaceous change.

Tuberculosis and cirrhosis.

Introduction.—Tuberculosis of the liver has little clinical importance, can seldom be diagnosed with certainty during life, and when found after death is usually part of generalised tuberculosis. Larger tuberculous

¹ Castellani and Chalmers. *Tropical Medicine*, 1910.

² *Vide* W. H. Dickinson. "Enlargement of the Viscera in Rickets," *Med.-Chir. Trans.*, Lond., 1869, lii, 359.

³ Hogben. *Birmingham Med. Rev.*, 1888, xxiv, 65.

P An endemic form of ^{intercellular} Cirrhosis with hepatic enlargement, ~~also~~ jaundice, and continued fever
but no splenomegaly has been described in Mexico (CARMONO y Valle).
Ascites is often present, and the disease runs a rapid course in 6 to 8 months.
which attacks
infants and young
children.

CARMONO y VALLE. Gaz. heb. d. de méd., Paris, 1897, N. S., II, 873.

Rollet

ROLLET. WIEN. KLIN. WCHSCHR., 1913, XXVI, 1274

masses seldom give rise to clinical manifestations. In the exceptional instances in which a tuberculous mass or abscess has produced enlargement of the liver, some commoner result of tuberculosis, such as fatty or lardaceous change, would probably be diagnosed. The comparative infrequency of advanced tuberculous changes in the liver might suggest that, like the thyroid gland, the liver is inimical to the growth of the tubercle bacillus. This, however, is doubtful, for in lower animals, especially in birds, hepatic tuberculosis is common, and Sergent¹ shewed experimentally that the bile is not more antagonistic to the growth of tubercle bacilli than of other micro-organisms. It is probable that the reason why advanced tuberculous changes are rare in the liver is that the liver does not, like the mesenteric glands, lie in the direct line of the lymphatic vessels conveying lymph from the intestines. The lymphatic glands in the portal fissure receive the efferent lymphatic vessels conveying lymph away from the liver. In order that tuberculous infection should pass into the liver along the lymphatics of the portal fissure the bacilli would have to work their way against the flow of lymph. Possibly this does occur, but in most cases in which the intestines, the liver, and the lymphatic glands in the portal fissure are tuberculous, the tubercle bacilli have probably travelled from the intestine to the liver by the portal vein, set up tuberculous foci in the portal canals, and so infected the lymphatic glands in the portal fissure.

Marmorek,² however, finds from experiment that there is a certain amount of immunity to tuberculous infection on the part of the liver which cannot be satisfactorily explained on the anatomical grounds mentioned above. He believes that chemical factors inhibit the growth of tubercle bacilli in the liver.

Paths by which Tubercle Bacilli can reach the Liver.—Tubercle bacilli may reach the liver from various sources.

By the Umbilical Vein.—During fetal life, if there is tuberculous disease of the placenta, the bacilli reach the liver by the umbilical vein. This is very rare and is chiefly interesting from Baumgarten's view that tubercle bacilli are retained in the liver from early fetal life in the form of spores. Experimentally tuberculosis of the liver in the fetus has followed local tuberculous infection of the genital organs in guinea-pigs (D'Arrigo³). Cases of hepatic tuberculosis in children within the first fortnight of life have been described (Sabouraud,⁴ Horl⁵), and are undoubtedly due to infection during fetal life. Bar and Rénon⁵ found tubercle bacilli in the blood of the umbilical vein of two fetuses of tuberculous mothers.

By the Hepatic Artery.—In generalised tuberculosis tubercle bacilli reach the liver by the hepatic artery. It is probable that tubercle bacilli often reach the liver when, although a number of bacilli have gained entrance to the general circulation, generalised tuberculosis does not result. Thus, in chronic

¹ Sergent. *Thèse de Paris*, 1895-6, No. 92; *Compt. rend. Soc. Biol.*, Paris, 1895, /1. xlvii, 351.

² Marmorek. *Arch. gén. de méd.*, Paris, 1903, ii, 2945.

³ D'Arrigo. *Centralbl. f. Bakt.*, 1900, xxviii, 683.

⁴ Sabouraud. *Compt. rend. Soc. Biol.*, Paris, 1891, xliii, 674.

⁵ Bar et Rénon. *Ibid.*, 1895, xlvii, 505.

pulmonary tuberculosis tubercles in the liver may be due to bacilli which have strayed into the blood-stream. The miliary tubercles are scattered through the liver both inside the lobules and in the portal spaces. It is possible that when a number of tubercles thus arise in the portal spaces they may increase in size and form a caseous mass which bursts into the bile-ducts and thus gives rise to the condition described as tuberculous cholangitis. Pilliet¹ suggested that tubercle bacilli might be excreted from the blood into the ducts and that tuberculous cholangitis then results. Microscopic examination, however, of such cases, viz. in which the ducts are involved (*vide* p. 341), shews that the tuberculous process always begins outside the ducts. It is only exceptionally that tuberculous cholangitis or abscess is due to bacilli reaching the liver by the arterial blood.

By the Portal Vein.—In tuberculous ulceration of the intestine tubercle bacilli readily pass by the portal vein to the liver, ~~and there set up either miliary tubercles, or the larger and more chronic tuberculous changes in connexion with the bile-ducts.~~ Tubercle bacilli can pass through the mucous membrane of the intestine without any gross lesion of the mucous membrane. A

By the Lymphatics.—In tuberculous peritonitis bacilli may possibly pass through the lymphatic vessels of the capsule into the liver. It is also conceivable that tuberculosis of the glands in the portal fissure, secondary to intestinal disease, might extend to the inside of the liver against the current of lymph.

By the Common Bile-duct.—It has been suggested that tubercle bacilli from the duodenum pass up the bile-ducts, work their way through the mucous membrane of the ducts into the portal spaces, and there give rise to caseous tubercles. This view, which is improbable as tubercle bacilli are non-motile, has been disproved by Sergeant's² injections of tubercle bacilli into the bile-ducts, which shewed that unless the walls of the ducts were previously damaged, as by ligature, they did not allow tubercle bacilli to pass through them. It is noticeable that the extra-hepatic ducts are not affected by tuberculosis except in the rarest instances, and that there is no condition of ascending or descending tuberculous cholangitis to correspond with tuberculous disease of the ureter.

To sum up: Tubercle bacilli reach the liver by the hepatic artery in generalised tuberculosis and in conditions which fall short of generalised tuberculosis. The portal vein also conveys tubercle bacilli to the liver, but there is no evidence that tubercle bacilli travel up the bile-duct and very little that hepatic tuberculosis is conveyed through the lymphatics.

Forms of Hepatic Tuberculosis

It might be thought more methodical to consider hepatic tuberculosis under two heads—(i) tuberculous disease of the liver substance proper and (ii) tuberculosis of the bile-ducts. But since, as will be shewn later, the ducts themselves are not affected primarily and only suffer as the result of extension from without, whether the starting-point is in the liver substance, the portal space, or in exceptional instances the lymphatic glands in the hilum, it is more practical to divide the subject of hepatic tuberculosis into—

¹ Pilliet. *Thèse de Paris*, 1891.

² Sergeant, E. *Thèse de Paris*, 1895, No. 92.

^ In so called primary tuberculosis of the spleen the liver is infected
in 80 p.c of the cases in which it is examined (Wintermütz)

Wintermütz. Arch. Int. Med., Chicago, 1912, ix, 680

Torrey in 63 percent
and white in 80 percent
of

Torrey. Am. Journ. Med. Sc., Phila.,
1916, CL1, 549
White. ~~Am.~~ Ann. Report. Henry Phipps
Institute, Phila., 1909. v, 376

(I) Miliary tuberculosis—(a) part of acute generalised tuberculosis; (b) due to infection from the intestine.

(II) Local tuberculosis—(a) involving the ducts; (b) not involving the ducts.

I. Miliary Tuberculosis

The presence of miliary tubercles in the liver is part of generalised tuberculosis, and though sometimes not seen on naked-eye examination, they will be found constantly in microscopic sections. Miliary tubercles are found in the liver in chronic pulmonary tuberculosis as a result of two processes: (a) tubercle bacilli reaching the liver by the hepatic artery, and (b) tubercle bacilli derived from secondary tuberculous ulcers in the intestine and passing to the liver by the portal vein.

Simmonds¹ found hepatic tubercles in 82 per cent of 476 cases of tuberculosis, 76 per cent in adults, 92 per cent in children. Zehden² found miliary tubercles in 50 per cent of all fatal cases of pulmonary tuberculosis, thus corresponding fairly with the ~~frequency~~ ^{incidence} of tuberculous ulceration of the intestine in that disease. My own experience would put the occurrence of miliary hepatic tubercles in fatal cases of ordinary pulmonary tuberculosis lower than 50 per cent.

Miliary tubercles in the liver at birth have been referred to on p. 337.

Morbid Anatomy.—Miliary tubercles in the liver are small and isolated, grey, and when older yellow in colour, and are better seen on the surface of the capsule than on section of the organ. In some instances the liver may be crowded with minute miliary tubercles which can only be seen when microscopic sections are made; to the naked eye the liver may merely shew cloudy swelling. In the substance of the liver the tubercles are nearly always situated inside the lobules and thus form a contrast to the local and chronic form of tuberculosis of the liver occupying the portal spaces. Miliary tubercles are not very rare in cirrhotic livers. The liver is generally fatty and rather increased in weight; there may be considerable venous engorgement from terminal failure of the right side of the heart. Usually there is little or no tuberculous perihepatitis, but this may coexist with miliary tubercles in the substance of the liver in two conditions: (a) When there is chronic tuberculous peritonitis in which the capsule of the liver shares, or (b) in rare instances a subacute fibrinous peritonitis associated with acute miliary tuberculosis of the capsule of the liver. It is possible that the miliary tubercles in the hepatic substance may, if the generalisation is not very acute, have time to unite into small caseous areas which may soften down and form small tuberculous abscesses.

In a child aged three months who died in St. George's Hospital with advanced tuberculous bronchopneumonia, the liver contained a large number of

¹ Simmonds. *Centralbl. f. Path.*, 1898, ix, 865.

² Zehden. *Ibid.*, 1897, viii, 468.

miliary tubercles and two tuberculous cavities stained with bile, rather larger than a pea. The intestines were free from tuberculosis. Sergeant described a unique case of confluent miliary tuberculosis of the liver.

Histology.—In their earliest stage tubercles consist of small round cells, like masses of lymphoid tissue, with a delicate reticulum. The cells are produced by proliferation of the connective-tissue cells; Metchnikoff regards the cells as phagocytes derived from vascular endothelium. After a time larger endothelioid cells are found in the miliary tubercle. When the tubercle grows larger, according to McWeeney,¹ 0.2 mm., giant cells appear. The giant cells are due to union of pre-existing cells, though it has been thought that continued growth and nuclear division without cellular division in endothelioid cells might account for them. The central part of the giant cells becomes homogeneous and caseous, while the nuclei form prominent objects around the periphery. It is often impossible to demonstrate bacilli in perfectly typical tubercles. The liver cells at the margin of the tubercles are compressed and may be fatty. In some cases the fatty change is widely diffused throughout the liver.

Signs and Symptoms.—There are *no clinical signs or symptoms* which can be relied upon to indicate the presence of miliary tubercles in the liver. Hilton Fagge², ~~and~~ Fränkel³ have seen it associated with jaundice, and recently Warthin⁴ states that some degree of jaundice is present in 80 per cent of the cases; this is quite contrary to general experience. A large number of tubercles on the surface of the liver may possibly give rise to a friction rub.

II. Local Tuberculosis

(a) Involving the bile-duets.

^{Masses} (b) Caseous tuberculous ⁵¹⁵ masses.

(c) Tuberculous abscess.

(a) Tuberculous Disease involving the Bile-duets

Synonyms: Tuberculous Cavities in the Liver; Tuberculous Cholangitis or Pericholangitis.

Incidence and Etiology.—Though this condition was described by Bristowe⁵ in 1858, who found it in 12 out of 167 cases of tuberculous ulceration of the intestines, it has not attracted much general attention, probably because it has no clinical features. It is a commoner condition than the number of recorded cases would suggest. The tubercle bacilli reach the liver by the portal vein, being derived from the intestines, which in most instances shew tuberculous ulceration. They settle down

¹ McWeeney. *Brit. Med. Journ.*, 1900, i, 844.

² Hilton Fagge. *Textbook of Med.*, 1886, ii, 270.

³ Fränkel, A. *Ztschr. f. klin. Med.*, 1882, v, 107.

⁴ Warthin. *Internat. Clin.*, Phila., 1911, s. 21, i, 89.

⁵ Bristowe, J. S. *Trans. Path. Soc.*, Lond., 1858, ix, 241.

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Milne, New York Med. Journ., 1913,

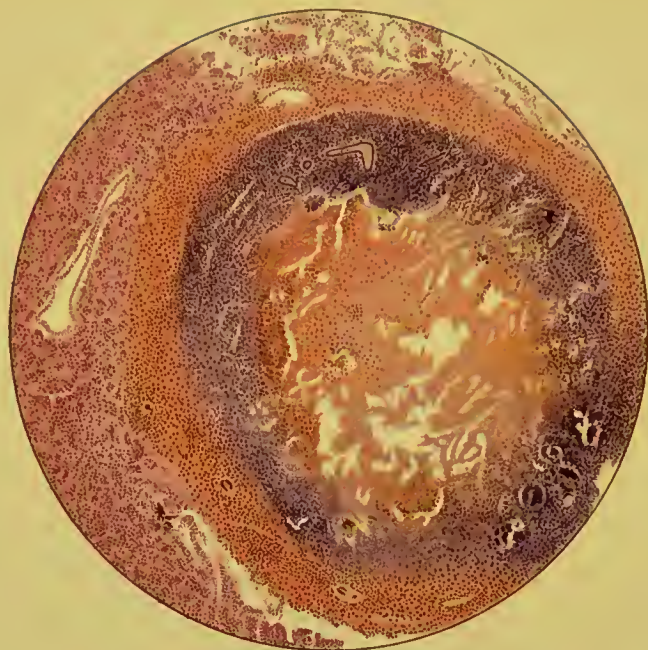
PLATE III.



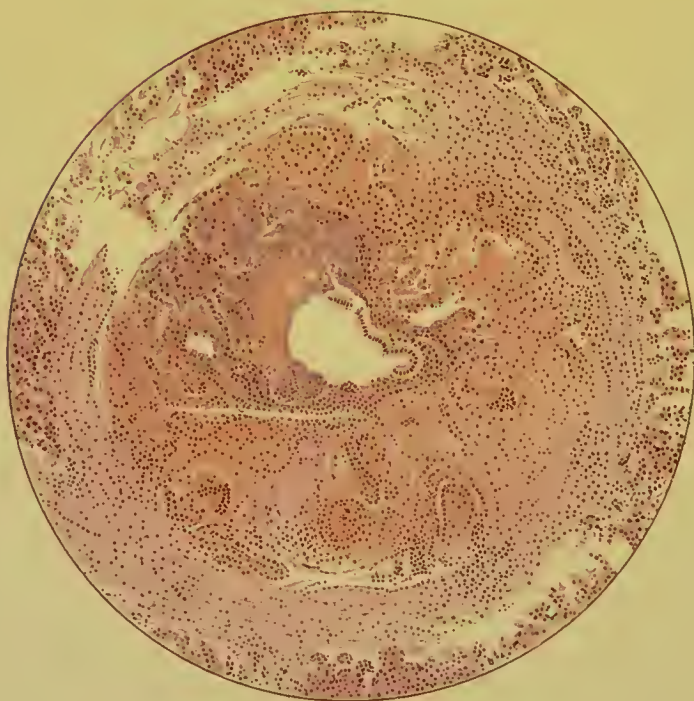
SECTION OF LIVER SHEWING TUBERCULOUS CAVITIES IN PORTAL SPACES, COMMUNICATING WITH THE BILE-DUCTS,
AND STAINED GREEN WITH BILE.

From a case recorded by Dr. Dudgeon. Painted by L. Jones, M.S.





1



2.

1. ADVANCED STAGE OF A TUBERCULOUS CAVITY IN THE LIVER.

There is a dense fibrous capsule derived* from the portal space which surrounds tuberculous granulation-tissue; more internally there is a mass of caseous debris.

2 Earlier stage, shewing tuberculous granulation-tissue occupying the portal space and opening into the bile-duct.

(These figures, from *Trans. Path. Soc.*, Lond. 1899, 1, 160, were kindly lent by Dr. Morley Fletcher.)





in the portal spaces and produce miliary tubercles, and later masses of tuberculous granulation-tissue. The condition might well be spoken of as tuberculosis of the portal spaces.

Sergent¹ insists that the first step is tuberculous pylephlebitis and thrombosis of the intrahepatic branches of the portal vein, and that at a later stage tuberculous granulation-tissue develops in the portal spaces.

The tuberculous granulation-tissue caseates, softens down, and eventually breaks into the bile-ducts from without inwards. The discharge of the tuberculous foci into the ducts is analogous to rupture of a caseous focus in the lung into the bronchi. The ducts become infected and may be entirely destroyed locally. The communication between the cavities thus formed and the ducts is not always visible, but from the bile-stained condition of the "vomicae" there can be no doubt this has occurred. (Compare Wethered's case.²)

As stress has been laid on the statement that the bile-ducts are invaded from without or are secondarily involved in tuberculous disease of the liver, it should be mentioned that Lancereaux³ described a case of tuberculosis of the common bile-duct, gall-bladder, and cystic duct in a woman aged thirty-two years, which he regarded as directly due to infection from the duodenum.

Morbid Appearance.—The liver is usually somewhat larger than natural, and on section shews a number of white caseous areas or of bile-stained cavities with caseous walls. In the earlier stages, before the tubercles have opened into the ducts, the tuberculous material is firm and resembles, and is therefore sometimes regarded as, lymphadenoma; in the later (excavation) stage, when they have opened into a bile-duct, their walls have a greenish-yellow colour from bile-staining, and exceptionally a purple colour from haemorrhage. In their early stage the tubercles may be $\frac{1}{6}$ to $\frac{1}{4}$ inch in diameter; the cavities subsequently formed are larger and may measure an inch or even two inches across.

Structurally the masses are enclosed in a capsule representing the fibrous tissue of the portal space, and contain caseating granulation-tissue surrounding a cavity which can be seen opening into a bile-duct; the epithelium of the bile-duct may be well preserved except at the point of perforation from without. The tuberculous process is therefore primarily pericholangitic, not cholangitic. Further, the bile-duct is not affected throughout its course in the way that a tuberculous ureter is, but is locally infected at the spot where it is invaded from without. The larger extrahepatic ducts are very seldom involved; a softened tuberculous gland in the hilum of the liver may exceptionally open into the bile-duct.

Köster⁴ has recorded a case which would bear this interpretation. A boy aged three years had jaundice, due to pressure of tuberculous portal glands, and

¹ Sergent. *Thèse de Paris*, 1895, No. 92.

² Wethered, F. J. *Trans. Path. Soc.*, Lond., 1889, xl, 139.

³ Lancereaux. *Traité des maladies du foie et du pancréas*, 1899, p. 662.

⁴ Köster. *Centralbl. f. inn. Med.*, 1896 xvii, 213.

tuberculous pneumonia. The liver contained tubercles, the ducts were dilated, and the lower end of the common bile-duct opened into a caseous cavity.

Macroscopic Diagnosis.—Tuberculous masses and cavities in the liver sometimes closely resemble other conditions. The deep bile-staining is extremely suggestive of tuberculous cavities in connexion with the bile-ducts, but before this staining has occurred the masses may resemble nodules of lymphadenoma, etc. The tuberculous masses are whiter and may break down, which lymphadenoma never does. In cirrhosis with multiple adenoma fatty change in the nodular areas of hyperplasia has often given rise to a mistaken diagnosis of tuberculous masses. In exceptional instances secondary carcinoma may closely imitate tuberculous masses and necessitate microscopic examination. The rare condition, chronic pericholangitis, of which Strangeways Pigg and I,¹ and Morley Fletcher,² have recorded examples, exactly imitates tuberculous cavities in the liver. Psorospermial disease of the bile-ducts in tame rabbits closely imitates tuberculous lesions, and though it is extremely rare in man, it is conceivable that some examples of this protozoan infection have been erroneously called tuberculous. Actinomycosis and the suppurating foci in pylephlebitis and cholangitis are hardly likely to be mistaken for tuberculous cavities, though abscesses at first regarded as tuberculous have been subsequently shewn to be actinomycotic.³ Cysts lined with epithelium and containing clear fluid may occur in tuberculosis of the liver (Merle⁴), and may be due to obstruction of the ducts exerted by the tuberculous tissue.

Histologically the portal space is occupied by tuberculous granulation-tissue containing giant cells and undergoing caseation. This surrounds the bile-duct and opens into it. Eventually the bile-duct may be destroyed, and at this stage the portal space contains a central mass of caseous debris, stained with bile and surrounded by tuberculous granulation-tissue.

Clinical Features.—There are very seldom any definite symptoms pointing to the liver. It is indeed remarkable that jaundice is constantly absent, inasmuch as there is very definite obstruction in, at any rate some of, the bile-ducts.

It seems possible that the reason why jaundice is not met with is that the lymphatic vessels which should carry the bile from the obstructed ducts are themselves compressed and are unable to convey the bile into the general circulation. If this be the case, the liver substance should be bile-stained. Since this does not occur in cases of tuberculous cavities in the liver, this explanation cannot be urged.

It is true that occasionally attacks of abdominal pain have been reported in cases in which tuberculous cholangitis was found after death. These attacks of pain are not accompanied by jaundice or by bile in the urine and are not likely to suggest biliary colic. The abdominal pain is

¹ Rolleston and Strangeways Pigg. *Journ. Path. and Bacteriol.*, 1898, v. 221.

² Morley Fletcher. *Trans. Path. Soc.*, Lond., 1901, lii, 193.

³ Harley, J., *Med.-Chir. Trans.*, 1886, lxi, 135; Shattock, S. G., *Trans. Path. Soc.*, Lond., 1885, xxxvi, 260.

⁴ Merle. *Arch. de méd. expér. et d'anat. path.*, Paris, 1909, xxi, 353.



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very probably due to tuberculous ulceration of the intestines or concomitant tuberculous peritonitis. Ascites may result from tuberculous peritonitis, or conceivably from compression of the portal vein by enlarged tuberculous glands. As a rule, the clinical aspect of the cases presenting this condition after death is that of pulmonary, abdominal, or generalised tuberculosis.

I examined after death a child aged nine months who had advanced tuberculous disease of the lungs, tuberculous ulcers in the intestine, caseous mesenteric glands, and tuberculous cavities in the liver. During life the signs were those of consolidation of the lungs ; there was no diarrhoea or jaundice. Winternitz ¹ records a case of tuberculous cavities in the liver associated with tuberculous ulcers of the stomach. In Dudgeon's specimen of tuberculous cavities in the liver (*vide* Plate III) from a girl aged two years, there were tuberculous ulcers in the intestine, tuberculous peritonitis, and adenitis of the lymphatic glands in the portal fissure.

Masses
(b) ^{SIS} Caseous Tuberculous Masses

Under this heading it will be convenient to consider comparatively large masses of caseous material which do not communicate with the bile-ducts. It is true that such masses might soften down and effect a fistulous communication with the bile-ducts, but it would then be impossible to be certain that the tuberculous process had not started near the bile-ducts. Although sometimes called "solitary tubercle," there may be a number of these caseous masses in the liver. This form of local tuberculosis, in which the portal spaces and bile-ducts are not specially involved, is rare, but is common in some animals.

Masses of hard caseous tubercle are very common in birds ; in fact, the liver is the chief, and in 20 per cent of the cases examined by W. Hutchinson² the only, organ affected in avian tuberculosis. In bovines large caseous masses are found in the liver ; they soften from suppuration and have a thick fibrous capsule.

Cases in man have been recorded by Craven Moore, Clement, Zehden, Simmonds (2), Fischer³ (2), Thayer,⁴ Felberbaum.⁵ I have certainly seen two. F. Craven Moore's⁶ case was extremely interesting in that there were 8 tuberculous masses in the liver of a man who died with carcinoma of the pylorus. It was thought that the tubercle bacilli were absorbed from the ulcerated surface in the stomach and that the absence of HCl in the gastric juice rendered this infection more feasible. Clement⁷ described an almost exactly similar case. Inasmuch as tubercle bacilli were not found in Moore's or Clement's cases, the possibility arises that there may have been some other cause for the caseous masses, such as the pseudo-tuberculosis bacillus described by A. Pfeiffer and by

¹ Winternitz. *Johns Hopkins Hosp. Bull.*, 1908, xix, 223.

² Woods Hutchinson. *Studies in Human and Comparative Pathology*, p. 304.

* Fischer. *Arb. a. d. Geb. der path. Anat. und Bakteriolog.*, Leipz., 1908, vi, 621.

⁴ Thayer. *Bull. Johns Hopkins Hosp.*, Balt., 1911, xxii, 146.

⁵ Felberbaum. *Med. Rec.*, N.Y., 1911, xxx, 1248.

⁶ Craven Moore. *Med. Chronicle*, 1899, 3. s., ii, 5.

⁷ Clement. *Virchows Arch.*, 1895, cxxxix, 35.

Klein. Klein¹ found a bacillus in Thames and Lea water which produced caseous masses in the liver, lung, and lymphatic glands.

The following are examples of multiple tuberculomas in the liver :

A boy aged eight years was admitted under my care in St. George's Hospital with pericarditis and advanced renal disease ; he recovered from the pericarditis, and multiple tuberculous lesions of the limbs, skull, and vertebrae gradually appeared. It was noticeable that as the tuberculous lesions advanced his renal symptoms receded. There was never any jaundice. He eventually died of exhaustion. The liver (20 oz.) was much enlarged as compared with his emaciated body. There was tuberculous perihepatitis with large white caseous masses, unstained with bile, in the liver. They were the size of filbert nuts and had been felt during life. No communication with the bile-ducts could be made out ; the mesenteric, tracheal, inguinal, and axillary glands were also tuberculous.

Milian and Hertz² recorded the case of a man aged fifty-eight with emaciation, an enlarged spleen, and fever unaffected by quinine. The clinical aspect suggested malaria or tuberculosis, but no signs were found in the lungs. The liver contained miliary tubercles and others as big as a horse-chestnut ; the spleen was also affected ; but there were no tubercles in the alimentary canal or lungs. In a somewhat similar case—a woman aged sixty-six years—described by Tolot,³ there were no intestinal or pulmonary lesions.

Around the white caseous masses there is a thin fibrous capsule, and outside this the liver substance is compressed and the cells elongated and flattened. The caseous masses may be fairly easily enucleated. They closely resemble gummas, and must be distinguished from the appearance presented in nodular hyperplasia when fatty degeneration has occurred in the hyperplastic liver cells. In a few instances encysted caseous masses have also been found in the spleen (Milian and Hertz ; Tolot).

The clinical aspect, as has been shewn by the foregoing cases, is not characteristic. The liver may not be made out to be enlarged. Exceptionally a tuberculous mass may be sufficiently large to be felt through the abdominal walls during life. In Bunzl's⁴ case there was so much pain that operation was necessary.

Thus, in a case related by T. L. Anderson⁵ a mass the size of a tangerine orange in the left lobe of the liver was distinctly felt during life. The patient, a man aged forty-one, had extensive intestinal tuberculosis.

In a few cases the spleen is palpably enlarged. Jaundice is most exceptional ; ~~it occurred in Thayer's case, which~~ was thought to be one of malignant disease ; a diagnosis can hardly be made. As a rule, the patients suffer from increasing weakness, loss of appetite, and general debility. *The disease may imitate enteric fever.*

¹ Klein, E. E. *Lancet*, 1899, ii, 1297.

² Milian et Hertz. *Bull. Soc. Nat.*, Paris, 1900, lxxv, 153.

³ Tolot. *Lyon méd.*, 1902, xcix, 323.

⁴ Bunzl. *München. med. Wchnschr.*, 1908, lv, 451.

⁵ Anderson, T. L. *Australas. Med. Gaz.*, 1899, xviii, 93.

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may occur towards the end

Milne, New York Med. Journ., 1913, xcvii, 978.

Excision of a tuberculous mass has been carried out with success (Rome,¹ Bunzl, Ransohoff²).

(c) Tuberculous Abscess

The caseous masses may become secondarily infected with pyogenic micro-organisms, soften down, and form abscesses; this occurred in H. Mackenzie's³ case, in which the cavities were purple and contained blood but not bile. In rare instances tuberculous abscesses may reach a considerable size, and cause local perihepatitis or even perforate into the peritoneal cavity. A tuberculous abscess of the liver may be either entirely inside the liver, or when near the surface of the organ may set up a localised perihepatic or a subphrenic abscess. A single tuberculous abscess of the liver is very rare. Some of the cases that have not been examined microscopically may have been softened gummas or actinomycotic abscesses (*vide* p. 386). A tuberculous abscess closely simulating actinomycosis is in the Pathological Museum of the University of Birmingham.

Mayo Robson⁴ operated upon a tuberculous hepatic abscess which was evidently single, as the patient was in good health more than two years afterwards.

There may be other evidences of tuberculosis in the body, such as advanced pulmonary disease, or, on the other hand, the liver may be exclusively or almost exclusively affected. Tuberculous abscesses are usually small and multiple and belong to the group of local tuberculosis involving the bile-ducts.

Effects on the Liver of Tuberculosis elsewhere in the Body

Tuberculosis elsewhere in the body may lead to other changes in the liver besides the secondary development of tubercles.

1. Focal necrosis and coagulation-necrosis due to the virulent action of bacilli on the liver cells; this has been studied experimentally by Pilliet and is the same as that described by Hanot in other infective disorders.

2. Fatty change. The fatty liver met with in pulmonary tuberculosis is well known. It is discussed on page 427.

3. Lardaceous change is not uncommon in advanced cases with long-continued suppuration. This change is due not to the tuberculous toxin, but in all probability to toxins derived from secondary infection of tuberculous abscesses or vomicae with pyogenic cocci.

Tuberculosis and Cirrhosis

As has been already pointed out, portal cirrhosis is frequently complicated by tuberculosis. It has, however, been thought that tuberculosis

¹ Rome. *Ann. Surg.*, 1904, xxxix, 98.

² Ransohoff. *Med. News*, N.Y., 1904, lxxxiv, 727.

³ Mackenzie, H. W. G. *Trans. Path. Soc.*, 1890, xli, 156.

⁴ Mayo Robson. *Trans. Clin. Soc.*, Lond., 1895, xxviii, 83.

may cause hepatic cirrhosis; in dealing with this question it will be clearer to consider it under two heads:

(A) Cirrhosis of the liver associated with tuberculosis of the liver.

(B) Cirrhosis of the liver associated with tuberculosis elsewhere, but not in the liver.

(A) *Cirrhosis associated with Tuberculosis of the Liver*.—In a patient with latent cirrhosis generalised tuberculosis may arise, and miliary tubercles develop in the liver in common with the other viscera. Tubercle bacilli may also be carried to a cirrhotic liver from the intestines. In children with nutmeg livers from backward pressure in heart disease, infection of the portal spaces with tuberculosis may supervene. The fibrosis is not great and the condition is essentially a complication of chronic venous engorgement of the liver; it is referred to under the name of “cardio-tuberculous cirrhosis” (p. 101). A large fatty cirrhotic liver containing miliary tubercles is sometimes seen. The two processes of hepatic cirrhosis and tuberculosis are probably independent of each other, but are both disposed to by alcoholism. Hanot and Gilbert¹ described a large fatty liver with small-celled infiltration and fibrous hyperplasia of the portal spaces and miliary tubercles as a morbid entity, due to tuberculosis, under the names “hypertrophic fatty tuberculous hepatitis” or “hypertrophic fatty cirrhosis.” Clinically there is enlargement of the liver, slight jaundice, and a little ascites, the disease running a rapid course in about six weeks. They further described two less acute forms of tuberculous cirrhosis: (a) Without any enlargement of the liver, and (b) with more fibrosis than in the previous form, but with similar fatty change and tuberculous infiltration. The two latter forms only differ in the fact that one shews marked nodules, like those seen in cirrhosis with adenoma. There is no doubt that these forms occur, but I believe that, generally speaking, the cirrhotic changes are not due to the tuberculosis. Around tuberculous masses in the liver there is local fibrosis which sometimes spreads diffusely into the surrounding liver tissue.

On the other hand, it is quite reasonable to believe that tubercle bacilli might, under certain conditions, such as high resistance of the liver or a low degree of microbic virulence, cause fibrosis in the liver just as in the lungs. This does not very often happen in man, since if the resistance of the liver is good or the vitality of the bacilli feeble, the latter would probably be destroyed outright. Still there are experimental grounds for believing that tubercle bacilli may under some conditions have a sclerogenic effect on the liver. Hanot and Gilbert² found that in guinea-pigs the bacilli of avian tuberculosis produced a markedly cirrhotic liver with deep scars, whereas tubercle bacilli from man induced fatty change and coagulation-necrosis (Pilliet³). Stoerk⁴ also produced a progressive fibrosis of the liver in guinea-pigs by the use of tubercle bacilli; at first there was definite tuberculosis of the liver, but as time went on the fibrosis advanced and the tuberculosis receded. Gougerot⁵ obtained much the same results. A small deeply scarred liver with lobulation and cicatrices like those of acquired syphilis was found by Hanot to be associated with scattered

¹ Hanot et Gilbert. *Arch. gén. de méd.*, Paris, 1889, clxiv, 513.

² *Idem.* *Compt. rend. Soc. Biol.*, Paris, 1892, xlv, 72.

³ Pilliet. *Thèse de Paris*, 1891.

⁴ Stoerk. *Wien. klin. Wchnschr.*, 1907, xx, 847.

⁵ Gougerot. *Rev. de méd.*, Paris, 1909, xxix, 81.

miliary tubercles in the substance of the organ. It resembles, in fact, the lesion produced in guinea-pigs by avian tubercle bacilli.

The following case, recorded by Collet and Gallavardin,¹ may perhaps be regarded as an example of cirrhosis due to tuberculosis. In a woman aged sixty in whom the spleen ($4\frac{1}{2}$ pounds) shewed massive tuberculosis the liver was greatly enlarged and contained small caseous tubercles in connexion with the portal spaces and a diffuse and rather delicate fibrosis. The hepatic changes were regarded as secondary to those of the spleen, and might be considered as an example of cirrhosis of splenic origin (*vide* p. 188). Isaac² described haemato-genous tuberculosis of the liver, lasting $3\frac{1}{2}$ years, and inducing cirrhosis.

(B) *Cirrhosis associated with Tuberculosis elsewhere, but not in the Liver.*—The association of hepatic cirrhosis and tuberculosis elsewhere in the body is common; in most cases in which the tuberculous process is active it has developed subsequently to the cirrhosis of the liver. In other instances there may be obsolete and latent tuberculosis of old date and independent cirrhosis of the liver, which are only discovered at the necropsy. In a certain number of cases old tuberculous lesions in the lungs are lighted up and make rapid progress in the course of alcoholic cirrhosis.

Nodular cirrhosis is sometimes found in fatal cases of pulmonary tuberculosis. Toxins generated in the lungs may lead to extensive fatty change in the proliferated liver cells forming the adenomatous projections on the cirrhotic liver. The appearance thus produced may imitate very closely that of multiple nodules of growth. It is conceivable that tuberculous lesions in other parts of the body may, by the production of chemical poisons, induce cirrhosis of the liver without any tuberculosis of that organ. Thus, in pulmonary tuberculosis, in which streptococcic infection of cavities is very common, toxins may be absorbed from the suppurating surfaces and carried to the liver by the general circulation. In most cases of such absorption from the lungs fatty degeneration of the liver, or even acute necrotic changes with toxæmic jaundice (Weber³), without any fibrosis, result; but in very chronic cases it is conceivable that cirrhosis might be brought about. Again, expectoration when swallowed may not only be the source of toxic bodies, which may subsequently be carried to the liver by the portal vein, but may set up gastro-enteritis and follicular, not necessarily tuberculous, ulceration of the intestines, and thus give rise to dyspeptic cirrhosis of the liver. Mouisset and Bonnamour,⁴ however, believe that cirrhosis in tuberculous patients is nearly always due to concomitant alcoholism. Lavenson and Karsner⁵ in 50 cases of tuberculosis of various parts of the body found some periportal fibrosis in 48, or 92 per cent, a higher percentage than in a number of control non-tuberculous patients; in 9 cases, or 18 per cent, the fibrosis was marked.

Hanot⁶ described lobulation of the liver in 7 cases of chronic tuberculosis and believed that fibrosis was due to the tuberculous toxin. I have notes of one such liver in a man with chronic phthisis in whom there was no history of syphilis and no gummas in the body; there was, however, a scar on the penis,

¹ Collet et Gallavardin. *Arch. de méd. expér. et d'anat. path.*, Paris, 1901, xiii, 191.

² Isaac. *Frankfurter Ztschr. f. Path.*, Wiesbaden, 1908, ii, 125.

³ Weber, F. P. *St. Barth. Hosp. Rep.*, 1908, xlv, 55.

⁴ Mouisset et Bonnamour. *Rev. de méd.*, Paris, 1904, xxiv, 337.

⁵ Lavenson and Karsner. *Univ. Penna. Med. Bull.*, Phila., 1909, xxii, 167.

⁶ Hanot. *Gaz. des hôp. de Paris*, 1893, lxvi, 902.

and there can be little doubt that it was in reality syphilis. Possibly some of Hanot's cases may have been examples of delayed hereditary syphilitic disease of the liver with secondary tuberculosis. At any rate, such a condition in tuberculosis pure and simple must be very rare.

In conclusion, although from a pathological point of view tuberculosis, both in the liver and when confined to some other part of the body, may in certain circumstances set up some fibrosis in the liver, there is no reason to think that genuine cirrhosis of clinical importance is primarily produced in this way. Tuberculosis, whether in the liver or elsewhere, may produce degenerative changes in the liver cells, and when there is pre-existing cirrhosis, considerable damage may be done in this way.

SYPHILIS OF THE LIVER

History.—That syphilis affects the liver is a very ancient idea; according to Frerichs,¹ as old as the history of syphilis itself. But the earlier views naturally differed from those of the present day. Fallopius² in the sixteenth century considered that the liver was primarily affected in syphilis and so corrupted the humours of the body that ulcers occurred on the genitals. Subsequently Morgagni opposed the view that the liver was affected in syphilis. Later van Swieten, Portal, and Ricord described syphilitic lesions of the liver, but very little attention was directed to the visceral lesions of syphilis until Dittrich³ in 1849, and S. Wilks⁴ in this country, described gummas in the internal organs. The distinction between gummas and nodules of malignant growth dates from this time; previously gummas were regarded as cancerous nodules or even as evidence of healing of malignant growths.

Syphilitic disease of the liver will be considered under the two main heads of (i) the acquired and (ii) the congenital ~~or hereditary~~ forms.

HEPATIC LESIONS IN ACQUIRED SYPHILIS

The hepatic changes due to acquired syphilis will be considered under the heads of (i) the secondary and (ii) the tertiary manifestations, while brief reference will be made to the possibility that remote—parasyphilitic—changes in the liver may be due to syphilitic infection.

The Secondary Manifestations of Syphilis in the Liver.—Diffuse intercellular cirrhosis similar to that of congenital syphilis occurs in the acquired form. But opportunities for examining the liver in the secondary stage of acquired syphilis are rare.

¹ Frerichs. *Diseases of the Liver* (Transl. New Sydenham Soc.), 1861, ii. 150.

² Fallopius. *Tract. de Morbo Gallico*, Padua, 1584.

³ Dittrich. *Vrtljschr. f. d. prakt. Heilk.*, Prag, 1849, 1; 1850, 33.

⁴ Wilks, S. *Trans. Path. Soc.*, Lond., 1857, viii, 240.

Fischl suggests that certain strains
of the spirochete may possess a special
affinity for the liver and quotes
cases in support of this hepatotropic
action

Fischl. Wien. med. Wochenschr., 1920, Lxx, 90.

Hermann Weber¹ many years ago described a case of acquired syphilis in a man aged twenty, in whose liver the lesions appear to have been intercellular. I have examined a few cases in which the liver of syphilitic subjects has shewn diffuse unicellular cirrhosis without any gumma.

Since then few cases are examined during the secondary stage, and since it is a lesion from which recovery is quite possible, it is not unlikely a priori that the condition occurs temporarily and usually passes away. In support of this it may be pointed out that in the rare cases of acute yellow atrophy supervening after syphilis the microscopical appearances are at least compatible with the view that there has been unicellular cirrhosis and that excessive necrosis of the hepatic cells has supervened.

In a man aged forty-seven, who died of cerebral haemorrhage and had gummatous testes, the liver shewed very diffuse intercellular fibrosis which varied in different areas, but was compatible with the views that there had been partial acute atrophy with recovery, or that it was intercellular cirrhosis. Dr. Parkes Weber,² who kindly shewed the slides to me, pointed out that the situation of the fibrosis, viz. around the capillaries of the hepatic artery, resembled that of lardaceous change and suggested that the poison was carried by the hepatic artery.³

In the secondary stage of acquired syphilis the liver may be affected so as to give rise to jaundice, either innocent or malignant; unicellular cirrhosis may occur, and in exceptional cases gummatous lesions are present (*vide* p. 360).

Jaundice in the Secondary Stage of Syphilis.—Jaundice may occur early in the secondary stage and at the same time as the cutaneous roseola. Paracelsus (1510) and Sanchez in the eighteenth century are credited³ with having noticed the association between early syphilis and jaundice, but our knowledge really dates from Gubler's⁴ memoir containing 5 cases in 1853. It is, however, uncommon, and more so in Germany than in France; in 15,799 cases of syphilis Werner⁵ met with jaundice in 57, or only 0·37 per cent; and Goldstein⁶ in 20 out of 7462 cases of syphilis, or 0·26 per cent. In 1868 Lancereaux⁷ collected 21 cases, and in 1900 Lasch⁸ referred to 49 cases, almost all from French literature. These figures suggest that jaundice during the roseolous stage is far rarer than it is in reality.

There are numerous views to explain the occurrence of jaundice in the early stages of syphilis. Inasmuch as it often coincides with the exanthem, it was first thought that it is due to a somewhat similar

¹ Weber, H. *Trans. Path. Soc.*, 1871, xvii, 152.

² Weber, F. P. *Brit. Med. Journ.*, 1899, i, 728.

³ *Idem.* *Proc. Roy. Soc. Med.*, 1909, ii (Path. Sect.), 116.

⁴ Gubler. *Mém. Soc. Biol.*, 1853, v, 235.

⁵ Werner, S. *München. med. Wchnschr.*, 1897, xlv, 736.

⁶ Goldstein. *Wien. med. Wchnschr.*, 1904, liv, 1861.

⁷ Lancereaux. *Syphilis*, 1868, i, 182; transl., New Sydenham Soc.

⁸ Lasch, O. *Berlin. klin. Wchnschr.*, 1894, xxxi, 904; *Selected Essays*, New Sydenham Soc. Library, 1900, p. 145.

condition in the mucous membrane of the bile-duct (Gubler); or, in other words, a specific cholangitis. A condyloma of the bile-duct has also been suggested. According to another view, pressure is exerted on the ducts by syphilitic enlargement of the lymphatic glands in the portal fissure; in favour of this it may be mentioned that out of Werner's 57 clinical cases of syphilitic jaundice there was marked enlargement of the superficial lymphatic glands in 41.

In Talamon's¹ case of acute yellow atrophy in a girl aged seventeen with a secondary cutaneous eruption and other signs of syphilis the glands in the portal fissure were enlarged but did not compress the common bile-duct (*vide p.*)

It has been thought to be ~~haemolytic in origin~~, and due either to increased fragility of the reds or to a haemolysin in the blood (Gaucher and Gougerot²). It is probably not simple catarrhal jaundice occurring in a person who has recently contracted syphilis, since the successful treatment is that of syphilis and not of catarrhal jaundice. But it might be due to changes in the small intrahepatic bile-ducts caused by general syphilitic hepatitis. When this intercellular infiltration is excessive, it may run on into acute yellow atrophy; about 50 cases of this severe sequel have been recorded, only 10 being in males (Fischer³; *vide* also p. 577). There is no proof that the jaundice is due to the ~~administration of mercury~~, for in only 4 of 49 cases of benign jaundice occurring in the early stage of syphilis, collected by Lasch, had mercury been given before the icterus appeared.

Sex.—In Lasch's 49 cases 25 were men and 24 women, but ~~as more cases of syphilis are seen in men~~, syphilitic jaundice is proportionately more frequent in women.

Its onset is usually sudden without any apparent cause and is not accompanied by any special disturbance, such as is seen in cholelithiasis or catarrhal jaundice. It comes on simultaneously with the cutaneous roseola and may coincide with a particularly copious eruption. It may appear as soon as five weeks after infection, or later up to the sixth month.

Clinical Features.—The jaundice is well marked, and unless treated with mercury, tends to become chronic; thus it may last three months if treated with the ordinary remedies for catarrhal jaundice. The aspect of the patient with a jaundiced syphilitic eruption is very characteristic and somewhat repulsive. There is an absence of gastro-intestinal symptoms and of itching; the appetite is well preserved, though distaste for fatty food may be experienced. The liver is usually slightly enlarged and the spleen may be palpable. In two exceptional cases there was transient ascites (Quinke,⁴ Gembarski⁵). Bile is absent from the urine or only temporarily present.

¹ Talamon. *Méd. mod.*, Paris, 1897, viii, 97.

² Gaucher et Gougerot. *Ann. des mal. vén.*, Paris, 1911, vi, 326.

³ Fischer. *Berlin. klin. Wchnschr.*, 1908, xlv, 905.

⁴ Quinke. *Die Krankheiten der Leber*, Wien, 1899.

⁵ Gembarski. *Rev. de méd.*, Paris, 1910, xxx, 689.

^ | the result of the direct action of the toxin on the liver cells, and others have regarded it as

It has been considered to be due to disturbed function of the liver cells and not obstructive or haemolytic (Brulé; Arden-Daltet, Derrien and Azoulay).

Brulé et Longevin. Bull. et mém. Soc. méd. des hôp. de Paris, 1916, 3^e sér., XL, 1851
Arden-DALTEY, DERIEN, et AZOULAY. Ibid., 1922, 3^e sér., XLVI, 221

hypersensitiveness of the
granulomatous cells to

Diagnosis.—The important point is to recognise that in a patient with recent syphilis jaundice may be a specific manifestation and not an independent attack of catarrhal jaundice. From the presence of the roseola and enlarged glands the recognition of syphilis is easy.

The *prognosis* is good, as a rule, but in some rare cases the jaundice passes into acute yellow atrophy. There are probably intermediate grades between the benign jaundice and the acute yellow atrophy occurring in the early stage of syphilis.

The *treatment* is that of secondary syphilis; it is noteworthy that the ordinary treatment of catarrhal jaundice is without any good result. If the mercurial treatment is prematurely discontinued, jaundice may recur.

The Tertiary Lesions of Syphilis in the Liver.—The specific tertiary lesions in the liver are polymorphic and include gumma, gummatous infiltration, cicatrices, and a combination of gummas and cicatrices (sclero-gummatous form). Lardaceous disease, which may be considered as a parasyphilitic lesion, is often combined with gummas and with cicatrices.

The manifestations of tertiary syphilis in the liver may be divided into (*a*) those that are progressive and (*b*) those that are merely the relics of past syphilitic activity. In other words (*a*) the late secondary and tertiary lesions seen in the gummas and gummatous infiltration of the organ and (*b*) the cicatrices, calcified remains, and deformities left behind by the first-named lesions are both included under the tertiary manifestations. Lardaceous disease, which is a sequel of syphilis, is dealt with elsewhere (*vide* p. 433).

Gumma.—The word gumma was employed in its present sense by Fallopius in 1584. But it was not generally used until comparatively recent times. In 1852 Budd¹ described gummas under the name of “encysted knotty tumours of the liver,” and separated them from cancerous growths, with which they had been generally confounded, but did not recognise their syphilitic origin or speak of them as gummas.

Method of Formation of a Gumma.—The early stage of the future gumma is a mass of syphilitic granulation-tissue of a pink colour, sharply localised, and contrasting with the healthy liver substance. At this stage it is better to speak of it as a syphiloma, since the word gumma describes a caseous mass surrounded by a fibrous capsule. After a time necrosis occurs in the centre of the syphiloma; this is partly due to syphilitic endarteritis in the neighbourhood whereby the blood-supply is cut off, so that the process has been compared to infarction (Beriel and Laurent²), and probably in part to ~~an increase in amount or concentration of the syphilitic poison.~~ At this stage there is a yellowish-white centre surrounded by pink granulation-tissue. Later there is a caseous mass surrounded by a fibrous capsule, a condition resembling a caseous

¹ Budd. *Diseases of the Liver*, 1852 ed. ii, 407.

² Beriel et Laurent. *Lyon méd.*, 1910, cxiv, 1291.

tubercle of some duration. By the union of several gummas a large gummatous area may result.



FIG. 41.—A large gumma of the liver extending through the diaphragm into the lower lobe of the right lung. From a specimen (Series ix, 183 g) in St. George's Hospital Museum.¹

Structure, etc.—A well-marked gumma consists of a firm, yellowish-white mass, not unlike the section of a potato, surrounded by a fibrous capsule which spreads out for a short distance into the surrounding liver tissue. In rare instances the caseous part of a gumma is yellow from

¹ I am indebted to Professor S. Delépine for this block, which appeared in the *Transactions of the Pathological Society of London*, 1891, xlii, 151.

Florand and Girault describe a
gemma in the left lobe adherent
to a similar formation in the
pre-pyloric part of the stomach.

Florand et Girault. Presse Méd., Paris, 1921.
p. 841

bile-staining (Marie¹). There are thus three zones in a gumma: (1) The central area of necrosed or necrosing granulation-tissue; (2) the surrounding fibrous capsule; (3) the invasion of the surrounding parts of the liver by interstitial fibrosis.

Old gummas consist of the central caseous portion and the well-formed fibrous capsule without any advancing margin. In recent gummas in which the capsule is indefinite there is, on the other hand, well-marked infiltration of the liver tissue.

The amount of fibrous tissue enclosing a gumma varies; in large and advancing gummas it may be slight and indistinct, in old gummas it is firm and dense. As it contracts it presses on the caseous centre, and at the same time, if near the capsule of the liver, produces thickening, puckering, and cicatrices on the surface of the organ. Peri-hepatitis and thickening of the capsule are thus produced; in rare instances, of which an example is given on page 165, there may be chronic universal perihepatitis. Adhesions frequently form between the liver and adjacent organs, the diaphragm, and the anterior abdominal wall; in rare instances gummas may behave like malignant tumours and invade the anterior abdominal wall, the diaphragm, or adjacent organs.

In a specimen (series ix, 183 g) in St. George's Hospital Museum an immense gumma of the right lobe of the liver passed through the diaphragm and extensively infiltrated the lower lobe of the right lung (Delépine and Sisley²; *vide* also Fig. 41). In a case reported by Bruhl and Lyon Caen³ a softened gumma put a bile-duct and bronchus into communication and so gave rise to a broncho-biliary fistula. In a case of late hereditary syphilis with the usual tertiary changes, recorded by Post,⁴ gummatous inflammation extended into the anterior abdominal wall and produced a definite tumour. A

Gummas are usually in the substance of the liver; occasionally, however, they project from the surface of the organ. To the naked eye gummas may sometimes closely resemble primary massive carcinoma or multiple carcinomatous growths in the liver.

Gouget⁵ described a case in which columnar-celled carcinomatous growths were at first thought to be gummas; I have seen similar appearances on several occasions. As a rare coincidence secondary growths may occur in a liver containing gummas. Microscopical examination is necessary before deciding that both gummas and secondary new-growths are present. In 1891 I examined such a case; a man had primary carcinoma of the colon with small secondary growths in a scarred and gummatous liver. The left testis also contained gummas.

1. c / ¹ Marie, R. *Bull. Soc. Anat.*, Paris, 1901, lxxvi, 628.

² Delépine and Sisley. *Trans. Path. Soc.*, 1891, xlii, 141.

³ Bruhl et Lyon Caen. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1909, xxviii, 295.

⁴ Post. *Boston City Hosp. Rep.*, 1898, p. 233.

1. c / ⁵ Gouget. *Bull. Soc. Anat.*, Paris, 1898, lxxiii, 605.

The *microscopic appearances* of a gumma differ according to its age. In the stage when caseation has begun, the central necrotic part, which to the naked eye appears white, is fibrillar or granular, shews a few nuclei but is otherwise structureless, and does not stain properly ; around it there is a mass of cells due to proliferating fibroblasts, and containing lymphocytes, plasma cells, and occasionally eosinophil and giant cells. These giant cells, which are rare in gummas, are formed from the endothelium of the small blood-vessels and possibly lymphatic vessels. The giant cells in gummas are not so large as in tuberculosis. Necrosis and caseation may be seen to be extending into this surrounding granulation-tissue in young gummas, while in older ones organisation is going on and

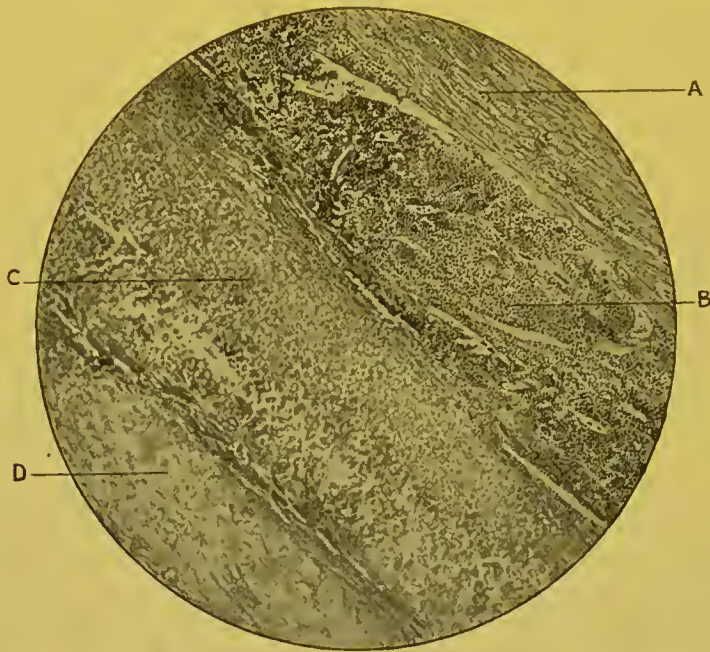


FIG. 42.—Recent gumma of liver. $\times 30$. A, Fibrous capsule ; B, syphilitic granulation-tissue ; C, caseating granulation-tissue ; D, caseous centre.

a capsule of connective tissue is formed around the caseous mass. The fibrous capsule contains elastic fibres and globules of fat.

The granulation tissue spreads into the surrounding liver tissue for a short distance, so that there is intercellular cirrhosis in the immediate neighbourhood of the gumma. Later groups of liver cells become surrounded by bands of young connective tissue, and in recent cases the solid columns of small cubical cells (pseudobile canaliculi) which stain deeply are prominent objects at the margin of a gumma. The liver cells near the margin of a gumma are flattened from pressure and may be spindle-shaped. The *Treponema pallidum* may be found at the margin of the necrotic areas.

The small arteries at the margin of a gumma shew well-marked endarteritis obliterans. There is sometimes lardaceous change immedi-

ately around the gumma. In old gummas which are no longer advancing, the fibrous capsule is dense and well formed, there is no small-celled infiltration around the gumma, and no giant cells. The caseous material and the proliferating zone around it contain a good deal of fat and thus differ from tuberculous caseation, in which fatty change is slight, the degenerative change being of a hyaline nature (Gaylord and Aschoff¹). Bile-stained cavities are very rare; they may be due to escape of bile into a softened gumma, or may be the outcome of a gummatous pericholangitis (Brault and Legry²).

Retrogressive Changes in Gummas.—The caseous material may diminish



FIG. 43.—Old gumma of liver. The lighter part is the caseous material; it is surrounded by a dense fibrous capsule which extends into the surrounding liver substance. (Photomicrograph by Dr. S. G. Penny.)

in amount from the circumferential pressure exerted upon it by the contraction of its fibrous capsule; at the same time it becomes drier from absorption of fluid. Calcareous change is not very rare, but it is usually only in small particles which do not offer any real resistance to the knife. In these cases the presence of calcareous matter is best seen in microscopic sections. In other instances calcification is best seen in the capsule of the gumma (*vide* Cambridge Museum, Nos. 504, 505). In exceptional cases calcification is very prominent.

Dr. Fooks kindly sent me the liver of a woman aged fifty-nine who died in the Brentford Union Asylum, Isleworth, in April 1898. It weighed $31\frac{1}{2}$ ounces and was two-thirds the natural size. The surface was scarred and puckered all

¹ Gaylord and Aschoff. *Pathological Histology*, p. 95, 1902, Lond.

² Brault et Legry in *Manuel d'histologie pathologique*, Paris, 1912, iv, part ii, 899.

over, especially on the right side. These cicatrices were all calcified; a section of the organ exposed several calcareous masses the size of a walnut. The youngest case in which I have seen calcified gummas was in a girl aged nineteen years, who died from the effects of lardaceous disease in St. George's Hospital in 1905. The liver, 44 oz., contained two calcified gummas. A cicatrix was found on the genitals and there were no signs of congenital syphilis.

Targett¹ described diffuse calcification of the liver which probably supervened on gummatous change (*vide* Fig. 44). Calcification of the liver may in very rare instances occur independently of syphilis (*vide* p. 440) and is met with in animals.

Occasionally gummas soften down; this may very probably be the result of treatment with iodides, and be a stage in the process of absorption. It may also be due to infection, and when it occurs in a large gumma the condition is practically a chronic abscess.



FIG. 44.—Diffuse calcification of liver probably subsequent to gummatous infiltration. St. George's Hospital Museum, Series ix, 172 B. (Drawn by Dr. E. A. Wilson.)

Moxon² described a large gumma, which softened down and communicated with a bile-duct.

Unless the gumma is very large, it is slowly absorbed. This is carried on by autolysis and phagocytosis, and depends on the neighbouring blood-vessels and lymphatics being permeable and not obstructed by syphilitic changes. The more the gumma contracts, the more it resembles the scars and cicatrices which are in many cases the only remains of obsolete gummas. This probably accounts for the rarity of gummas in old persons. The scars may, however, result from the organisation of inflammatory products without any central caseation having taken place.

Number and Situation.—Gummas may be circumscribed and multiple, or there may be diffuse gummatous infiltration of a large part of one or even of both lobes. The right lobe is much more often affected and the anterior surface far more frequently than the under aspect. They are much more often multiple; in 100 cases of hepatic gummas collected by Tresawna³ only 11 were single. The liver of a soldier aged thirty-two, who had contracted syphilis ten years previously, weighed 67 oz. and contained small caseous gummas, estimated at 268 in number [St. George's Hospital Post-mortem Book, 1905, No. 334]. It is said that the neighbour-

¹ Targett. *Trans. Path. Soc.*, Lond., 1889, xl, 123.

² Moxon. *Ibid.*, 1872, xxiii, 153.

³ Tresawna, W. S. Unpublished Thesis for M.B. degree, Cambridge, 1907.

hood of the falciform ligament is a favourite situation for gummas, but I have not noticed any special localisation of gummas except the anterior surface. They may occur in any part and may, when near the portal fissure, press on the main trunks or branches of the bile-ducts or portal vein. In W. G. MacCallum's¹ case a gumma in the liver pressed on the inferior vena cava and gave rise to thrombosis.

Syphilitic Cicatrices.—Deep furrows on the surface of the liver, due to cicatricial contraction, are the result of organisation of syphilitic granulation-tissue. Cicatrices may be formed directly from syphilomas or be the last stage of a gumma which has undergone absorption. The



FIG. 45.—Liver with syphilitic cicatrices. St. George's Hospital Museum, Series ix, 174 e.

cicatrices may be linear or may be star-like. The linear cicatrices may divide a lobe into a number of lobules; the star-like cicatrices are depressed with well-formed fibrous tissue radiating into the capsule on all sides of it. The liver may be so widely fissured and lobulated by cicatrices that it has a slight resemblance to the coarse hobnailed liver of portal cirrhosis, but the irregularity of this diffuse syphilitic fibrosis, or "syphilitic cirrhosis," as it is often called, distinguishes it from genuine portal cirrhosis. Like gummas, these scars are said to be frequent in the neighbourhood of the falciform ligament. When they occur near the portal fissure, they may involve the portal vein, giving rise to ascites, or the bile-ducts, thus producing jaundice; or if they occur near the

¹ MacCallum. *Johns Hopkins Hosp. Bull.*, Balt., 1903, xiv, 88.

coronary ligament, they may lead to narrowing or obliteration of the hepatic veins (*vide* p. 50).

Bosanquet¹ records obliteration of the inferior vena cava by syphilitic cicatrices spreading from a gummatous liver.

The scars may contain a central caseous mass, shewing that they are receding gummas; sometimes calcification has commenced in the caseous material. The older the scar, the denser it is, and the more depressed the surface of the liver over it.

Gummas and Cicatrices combined (Sclero-Gummatous Form).—The contraction of syphilitic cicatrices and gummas may lead to great deformity, so that the organ is nodular and irregularly lobulated.

In a girl aged twenty-five years who died under my care in St. George's Hospital with syphilitic stenosis of both bronchi² the liver (52 oz.) was occupied by multiple caseous gummas and was so extensively scarred that as many as 16 lobes could be counted on its anterior surface.

The shape of the liver may be altered out of all recognition. The relative size of the two chief lobes of the liver may be greatly altered; thus, the left lobe may be almost entirely destroyed by fibrous contraction, or enlarged from gummatous infiltration or from hyperplasia of the liver substance to compensate for extreme destruction of the right lobe. Schorr³ and Milne⁴ have collected some cases of compensatory hypertrophy of one lobe when the other is destroyed by gummatous or cicatricial change. As a rule, the syphilitic lesions and enlargement are much more marked in the right than in the left lobe.

Association of Gumma and Lardaceous Change in the Liver.—As already pointed out, local lardaceous change may be found around a gumma. In other instances gummas may be found in a universally lardaceous liver. In 86 cases of gummas collected by J. L. Allen the liver was lardaceous in 12, or 14 per cent. In Flexner's⁵ 88 cases the liver was lardaceous in 7 or 8. In these 174 cases the percentage is 11·2.

Incidence of Gummas in Universally Cirrhotic Livers.—It might naturally be supposed, since alcoholic excess and exposure to syphilitic infection are frequently associated, that gummas would be common in universally cirrhotic livers. This, however, is not the case, and it is remarkable how seldom gummas and ordinary portal cirrhosis coexist in the same liver.

Among 174 cases of hepatic gumma, obtained by combining J. L. Allen and Flexner's cases, there were 13, or 7·5 per cent, with genuine cirrhosis. *two* Dr. Trevor has shewn me *A* universally cirrhotic liver containing several large gummas and adenomas, *A* *one*

¹ Bosanquet, W. C. *Edin. Med. Journ.*, 1902, N.S., xii, 250.

² Rolleston and Ogle. *Trans. Clin. Soc.*, 1899, xxxii, 158.

³ Schorr. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1907, xlii, 179.

⁴ Milne. *Journ. Path. and Bacteriol.*, Cambridge, 1909, xiii, 129.

⁵ Flexner. *New York Med. Journ.*, 1902, lxxv, 101.

1. ^{the other} ~~and also a universally circulating~~ (7 lbs.) containing
60 gummas.

Out of 3300 necropsies at
the Johns Hopkins Hospital
there were 21 gummas

Alcoholism may merely
act by favouring exposure
to syphilitic infection

McCrae, J. A. Jour. Amer. Med. Assoc., Phila.,
1912, 6: 625

Incidence of Tertiary Hepatic Lesions.—Though well recognised and exhaustively described, the tertiary hepatic manifestations are by no means very common. It is true that cicatrices of old gummas are usually entirely latent, so that they are less frequently detected clinically than in the post-mortem room. Cicatrices are apparently more often seen than gummas, though in many instances gummas and cicatrices are present in the same liver. But even in the post-mortem room they are rare.

In an examination of the post-mortem records of St. George's Hospital, dealing with a period of fifty years (from 1857 to 1906), J. L. Allen and W. S. Tresawna found 44 cases only of undoubted hepatic gummas; during this same period there were 13,960 necropsies; there were, in addition, 34 other cases in which cicatrices alone were present. Among 9500 necropsies at Guy's Hospital in the twenty years 1885–1904 there were 23 cases with gummas, and 72 with cicatrices (Hale White¹). Among 11,300 necropsies performed at the Middlesex Hospital between 1854 and 1900 gummas were noted in the liver in 40 cases.² In a period of thirty-five years during which there were 5088 necropsies at the Philadelphia Hospital, Flexner³ found gummas in 23 cases, cicatrices in 38, and in all 88 cases of hepatic syphilis, half this number being cases of diffuse syphilitic fibrosis. Thus, out of a total of 39,848 necropsies gummas occurred in 130 cases only, or 0.33 per cent. But when syphilitic lesions are found in the body after death the liver is affected in more than half the cases; in 87 such cases examined at Manchester the liver shewed syphilitic changes in 51, or 58.6 per cent (Brockbank⁴).

There is indeed a great contrast between the frequency of hepatic lesions in congenital and in acquired syphilis.

Predisposing Causes.—It has been thought that previous disease of the liver, or conditions such as alcoholism, malaria, or jaundice, would, by diminishing the resistance of the liver, render it more likely to be affected. Trauma, such as blows or previous injury to the liver, may very probably, as elsewhere in the body, determine the occurrence of gummas in the organ. It is interesting to note that gummas have been found in the pendulous portion of the right lobe seen in the tight-laced or corset livers of women. But hepatic gumma is more often seen in men than in women.

In 141 cases of gumma of the liver collected from various sources by W. S. Tresawna 100 were males and 41 females; he could not find any evidence that tight lacing disposed the liver to gummatous change.

It is difficult to prove the influence of injury in determining the incidence of gumma in the liver, but the greater frequency of hepatic gumma in the male sex, nearly 3 to 1, and on the anterior surface of the liver, certainly favours this hypothesis.

¹ Hale White. *Common Affections of the Liver*, p. 192, 1908.

² *Arch. Middlesex Hosp.*, 1905, v, 136.

³ Flexner. *New York Med. Journ.*, 1902, lxxv, 101.

⁴ Brockbank. *Med. Chronicle*, Manchester, 1909, 1, 319.

In a case recorded by Pitt¹ the irritation of an old hydatid cyst in the liver seemed to have determined an extensive syphilitic formation around it.

Age Incidence.—The great majority of hepatic gummas are found between the ages of twenty-five and fifty years. In 78 cases of hepatic gumma collected by J. L. Allen, 69, or 88·5 per cent, occurred within this limit. The average age of these 78 cases was thirty-nine years, and was almost the same in the two sexes. The cases were arranged as follows :—

Age.	Number of Cases.	Age.	Number of Cases.
15-20	1	46-50	11
21-25	2	51-55	3
26-30	15	61-65	1
31-35	10	66-70	1
36-40	21	71-75	1
41-45	12		

Gummatous disease in the liver has been observed at the advanced age of eighty-nine (Wagner²).

Interval between Infection and the Appearance of Gummas.—Usually several years, from ten to twenty, elapse between the primary chancre and evidence of gummas in the liver ; but exceptionally gummas have been found within a year of infection.

Key³ found a gumma the size of a walnut in the liver of a woman aged twenty-six who died of generalised tuberculosis six months after infection ; and Fleischhauer,⁴ a gumma in the liver of a man who died seven months after infection. These cases are analogous to the rare instances of hepatic gummas in fetuses and stillborn children (*vide* p. 370).

Clinical Manifestations.—Clinically the occurrence of manifestations due to hepatic lesions, apart from lardaceous disease, is comparatively rare in tertiary syphilis. *are*

Mauriac,⁵ combining the statistics of Fournier, Ehlers, and Hjalman, found that in 7497 cases of tertiary syphilis symptoms pointing to the liver occurred in only 41.

he rarely It is remarkable how rare syphilitic lesions in the liver are in cases of locomotor ataxia, and it has been suggested that there is some kind of antagonism between hepatic syphilis and parasymphilitic lesions of the nervous system. Gummas and especially cicatrices are not uncommonly latent, and are only found after death as a surprise.

The factors which determine symptoms are : (1) the size and extent and (2) the position of syphilitic lesions in the liver. (1) If a gumma is

¹ Pitt. *Trans. Path. Soc.*, Lond., 1886, xxxvii, 276.

² Wagner. *Arch. f. Heilk.*, 1864, v, 126.

³ Key. *Schmidts Jahrb.*, 1874, clxi.

⁴ Fleischhauer. *XII. Congr. f. inn. Med.*, Wiesbaden, 1893.

⁵ Mauriac. *Gaz. hebdom. de méd.*, Paris, 1888, 2. s., xxv, 564.

large, it will give rise to the signs of a tumour, and by irritating the capsule of the liver to perihepatitis and pain; the morbid metabolism inside it may lead to the production and absorption of poisons which cause constitutional symptoms, such as anaemia, asthenia, and fever. (2) A cicatrix or small gumma on the convexity of the liver may not cause any symptoms, but if situated in the portal fissure, jaundice and ascites may follow. There is a great difference between the relative importance of the symptoms produced by a caseous gumma and by an old cicatrix; for symptoms due to the pressure of a gumma may be relieved or disappear under treatment, whereas it is highly improbable that an old cicatrix will be influenced.

As just pointed out, there is usually a considerable interval (ten to twenty years) between the primary infection and the onset of symptoms; it may be postponed for thirty or forty years, so that it has been said that no one can be regarded as cured of syphilis until he has been examined after death. Some cases shew signs of hepatic involvement within three years of infection, and exceptionally hepatic symptoms develop with great rapidity. In the early stages of the disease, before very definite localising symptoms and signs appear, there is very commonly weakness, general loss of health, failure of appetite, and gastro-intestinal disturbance. According to Marcuse,¹ two-thirds of the cases shew gastro-intestinal symptoms in the early stages. As gummas nearly always reach the surface of the liver, local perihepatitis is common, which, according to its intensity, accounts for discomfort, pain, and tenderness in the right hypochondrium; the pain may radiate to the right shoulder, and is sometimes accompanied by local tenderness. Pain ~~is one of~~ the most frequent symptoms in tertiary syphilis of the liver. } and loss of weight are

The clinical manifestations of tertiary syphilitic disease of the liver are protean, and for convenience may be grouped under the following headings:—(I) With symptoms suggesting portal cirrhosis, or simple chronic peritonitis and perihepatitis. (II) Presenting widespread lardaceous disease. (III) Suggesting tumour of the liver, such as malignant growth, hydatid, or enlarged gall-bladder. (IV) Imitating suppuration in the liver. (V) Resembling cholelithiasis. (VI) Simulating chronic splenic anaemia. (VII) With clinical features resembling hypertrophic biliary cirrhosis. } and phos

I. Cases imitating Cirrhosis.—These cases are frequent and important, as they probably account for some of the reputed cures of ordinary cirrhosis. There is ascites which is serous, but in rare instances has been noticed to be chyliform (Veil, Galvagni,² Poljakoff³) or even haemorrhagic. Other signs of portal obstruction, such as haematemesis, dilated veins in the abdominal walls, and dyspepsia, are much less frequent than in cirrhosis. Among 42 cases of hepatic syphilis in which full clinical

¹ Marcuse. *Wien. med. Wchnschr.*, 1900, I, 2219.

² Veil, Galvagni. Quoted by Boix. *Arch. gén. de méd.*, Paris, 1903, cxcii, 1302.

³ Poljakoff. *Berlin. klin. Wchnschr.*, 1900, xxxvii, 9.

notes were available 2 only had had haematemesis (Tresawna). In a case reported by Ebstein¹ a necrotic gumma appeared to have given rise to extensive haemorrhage into the biliary system and melaena. There may be enlargement of the spleen. ~~Jundice is very infrequent.~~ Ascites may be produced in several ways: (i) by the pressure of cicatrices or gummas on the intrahepatic branches of the portal vein, or in some instances on the trunk of the vein in the portal fissure of the liver; there was hepatic syphilis in 7 out of 68 cases of portal thrombosis collected by Lissauer;² (ii) by constriction of the hepatic veins; (iii) by perihepatitis over gummas; this is usually local, but may be more widespread and give rise to some chronic peritonitis.

Under iodide of potassium the gumma undergoes absorption, and the symptoms will pass off unless there is enough cicatricial tissue left to exert permanent pressure on the portal vein or its branches. In a number of cases the absorption of the gumma leads to relief; these cases are responsible for some of the reputed cures of portal cirrhosis, for iodides are commonly given in that disease. In other instances in which there is no means of knowing that there is a firm cicatrix, and not a gumma, embarrassing the portal circulation, antisiphilitic treatment fails, and the case more closely resembles common cirrhosis.

The Differential Diagnosis of Syphilitic Disease of the Liver from Ordinary Cirrhosis.—The history and other signs of syphilis, including a positive Wassermann reaction, should always suggest a syphilitic disease of the liver and lead to adequate antisiphilitic treatment. In syphilis the liver may be irregularly enlarged, ~~especially the right lobe~~, while in cirrhosis enlargement is more uniform. ~~Definite enlargement of the spleen in the absence of lardaceous disease, which itself points to syphilis and should then be accompanied by albuminuria, is rather in favour of cirrhosis.~~ An alcoholic history and dyspepsia of long standing are also in favour of cirrhosis. Ascites which frequently recurs after paracentesis is probably not due to cirrhosis, but to chronic peritonitis and perihepatitis or to syphilitic disease of the liver. When ascites is due to cirrhosis, the patient is usually thin or emaciated, whereas in syphilitic disease of the liver nutrition may be fairly well preserved.

Cases resembling Simple Chronic Peritonitis and Perihepatitis.—Cases of ~~syphilitic disease of the liver~~ ^{hepatic} in which ascites recurs will closely resemble simple chronic peritonitis, of which chronic universal perihepatitis is only a part. Chronic and recurrent ascites only occurs in a certain proportion of the cases of hepatic syphilis, while it is constant in simple chronic peritonitis. There must, therefore, be undoubted evidence of syphilis, such as a positive Wassermann reaction, or enlargement and irregularity of the liver, which point to gummatous disease, before the diagnosis of syphilitic disease is made in preference to chronic peritonitis. A thorough course of iodides should, however, always be tried. But failure of this treatment does not absolutely put syphilitic disease out of court. Uni-

¹ Ebstein. *Deutsches Arch. f. klin. Med.*, Leipz., 1908, cxii, 236.

² Lissauer. *Virchows Arch.*, 1908, cxcii, 276.

Fatal haematemesis from an oesophageal varix occurred
in a man aged 29, whose liver contained a genuine hydatid
of the fetal head (Core), and from a gastric varix overlooking a dilated
splenic artery in a woman with a generalised peritonitis (Carnot)

dy (vide p 36)

j among ³5 cases of hepatic syphilis
the spleen was enlarged in 24 (McGee).

^ j in ⁴⁹50 cases of hepatic syphilis showing hepatic enlargement
the left lobe was strikingly involved as compared with the right (McGee).

CORE. Lancet, Lond., 1913, i, 677.

CARNOT, P. Bull. et mém. Soc. méd. des hôp. de Paris, 1910, 3^e sér., xlii, 7.

The liver may be ~~abnormally~~ generally
enlarged, may present numerous
nodules, or there may be a
rounded tumour

versal chronic perihepatitis may in some rare instances be associated with and possibly due to syphilis (*vide* p. 165). Cheadle¹ considered syphilis the most important cause of perihepatitis. My own experience is that gummas commonly cause local perihepatitis, but that syphilitic infection is quite an exceptional cause of universal perihepatitis. In 22 cases collected by Hale White² syphilis was the apparent cause in 3.

II. Cases with the Features of Lardaceous Disease.—When a gummatous liver is associated with lardaceous disease, the renal affection gives rise to albuminuria and dropsy, and the aspect of the case may be that of renal disease. In these circumstances the presence of a gumma in the liver may naturally be unsuspected. Albuminuria in syphilis is not, however, undeniable proof of lardaceous disease, since it may be due to a syphilitic nephritis. In some cases in which the liver and spleen are both very considerably enlarged, the clinical aspect has been described as that of Hanot's hypertrophic biliary cirrhosis but without jaundice (Boix³). The following is a well-marked case of syphilitic gummas of the liver combined with lardaceous disease :

A man aged forty-two years was under my care in St. George's Hospital, with ascites, albuminuria, and casts ; there was no ~~trace~~ of jaundice and his facial aspect was that of cirrhosis. There was no cardiac disease or hypertrophy ; the blood-pressure was low. It was thought possible that he had lardaceous disease of the kidneys and syphilitic disease of the liver, but the diagnosis was open to doubt, as there was no history or signs of lues veneris. The spleen could not be felt. The liver was somewhat enlarged. He was put on iodide of potassium, but without any improvement, and his abdomen was tapped ; a week later he vomited, complained of abdominal pain, and as there was considerable ascites, he was again tapped ; the fluid withdrawn was turbid and contained numerous pus corpuscles ; the patient rapidly died. At the necropsy there was recent peritonitis. The liver, 8 lb. 10 oz., was somewhat scarred, and shewed a gumma, the size of a cocoanut, in the posterior part of the right lobe, which compressed the right branch of the portal vein and had running through its centre a large bile-duct. There were other small gummas in the liver, which was lardaceous. The spleen (20 oz.) shewed diffuse waxy change. The left kidney was atrophied ; the right (15 oz.) was lardaceous.

III. Gummas, etc., imitating Hepatic Tumours.—The irregularities produced by gummas on the anterior surface of the liver may be readily felt through the abdominal wall. The elevations of the liver substance due to the contraction of cicatrices are also easily palpable. A large gumma or gummatous infiltration of a lobe or part of a lobe may suggest primary massive carcinoma. If a Wassermann reaction is positive, iodides and mercury should be given in full doses. Jaundice and ascites, especially together, are more likely to be met with in malignant disease ; other points in favour of growth are rapid increase in the size of the liver, marked constitutional symptoms, and signs of a growth elsewhere. In a

¹ Cheadle. *Some Cirrheses of the Liver*, pp. 41, 43, 1900.

² Hale White. *Allbutt's System of Medicine*, 1897, iv, 121.

³ Boix. *Arch. gén. de méd.*, Paris, 1903, xcii, 1302.

syphilitic subject an enlarged and irregular liver may be due either to gummatous disease or to new growth, for syphilis in no way protects against malignant disease. ¹ The vigorous administration of iodides and mercury should decide the question, diminution in size of the liver settling the diagnosis in favour of gumma.

An eminent member of the medical profession who had been unfortunately inoculated with syphilis died with hepatic cancer, which he had naturally at first hoped and believed to be gummatous disease.

Enlargement of the spleen, from lardaceous or gummatous change, is more likely to accompany syphilis than malignant disease of the liver. When gummas are associated with lardaceous change in the same liver the enlargement may be extreme, and the resemblance to carcinoma very close. The irregularities produced by cicatrices in a lardaceous liver also imitate malignant disease. In such cases albuminuria points to lardaceous disease, and is therefore in favour of syphilis. Moreover, albuminuria is rare in malignant disease of the liver.

A man aged forty-one who had had a sore on the penis followed by a bubo, but no other history or signs of syphilis or suppuration, was admitted to St. George's Hospital with ascites and albuminuria. After tapping, nodules were felt on an enlarged liver and the tentative diagnosis of cirrhosis was given up in favour of malignant disease. At the necropsy the irregularities felt as nodules were due to peritoneal adhesions over the convexity of the liver; the liver weighed 9 lbs., was fatty and lardaceous, but presented no fibrosis, gumma, or growth. The spleen (13 oz.), kidneys, suprarenals, and intestines were lardaceous. One testis shewed fibroid change.

Difficulty sometimes arises in deciding between gummatous infiltration of a lobe of the liver and a *hydatid cyst* embedded in the liver. The general health in hydatid is unaffected, unless suppuration has occurred, and the liver is smooth, whereas in syphilis, a positive Wassermann reaction, other signs of the disease, and irregularity of the liver should be present. In any doubtful case iodides should be given at once. Gummatous and cicatricial deformity of the right lobe may suggest malignant disease of the gall-bladder. A gumma projecting from the liver close to the gall-bladder may also suggest a primary carcinoma of the latter viscus. A gumma in the left lobe of the liver may imitate carcinoma of the stomach. Gummas, when adherent to the stomach, may cause much dyspepsia (Curtis¹).

may/ ^h IV. Cases with Fever, resembling Hepatic Suppuration.—Occasionally irregular fever occurs in gummatous disease of the liver,² and may perhaps be due to secondary infection of a gumma. ^h The fever may suggest hepatic suppuration, pyelephlebitis, malaria (Cabot³), latent tuber-

¹ Curtis. *Clin. Journ.*, Lond., 1911, xxxviii, 43.

² Bristowe, *Trans. Clin. Soc.*, Lond., 1886, xix, 249; Gerhardt, *Berl. klin. Wchnschr.*, 1900, xxxvii, 1046; Klemperer, *Ztschr. f. klin. Med.*, 1904, lv, 177; Weber, F. P., *Lancet*, Lond., 1907, i, 728 (Bibliography); Breccia, *Riv. crit. di clin. med.*, Firenze, 1907, viii, 665, 692; Edwards, *Amer. Journ. Med. Sc.*, Phila., 1910, cxl, 527; Riley, *Trans. Chicago Path. Soc.*, 1911, viii, 91 (References).

³ Cabot. *Journ. Am. Med. Assoc.*, Chicago, 1910, lv, 1343.

1 | ~~Case of~~ Carcinoma arising in a anasthetic liver thought to be syphilitic is recorded
by Menetrier,
Yamagiwa,

1 | Mc Crae found some tumor in 49 out of 56 cases

YAMAGIWA. Virchows Arch. 1911, CCVI, 437

Menetrier. Bull. et mém. Soc. méd. des hôp. de Paris, 1917, 3^e ser., XLI, 1253.

Leukocytes is absent
 hepatic syphilis; in 30
 cases the average white
 count was 8400 (see case).
 In Trabaud's case the leukocyte
 count showed 8 per cent. of eosinophils.

it occurred in 23 out
 of 56 cases of tertiary
 hepatic syphilis (McCrae)

A gumma in close proximity to a
 calcareous gall-bladder imitated
 carcinoma of the gall-bladder (Wakeley)

GILBERT, CHIRAY, et COURY. Bull. et mém. Soc. méd. des hôp. de
Paris, 1921, 3^e ser., XLVI, 417.

MCCRAE, T. Am. Journ. Med. Sc., Phila.,
 1912, CXLIV, 625

TRABAUD. Bull. et mém. Soc. méd. des hôp. de Paris,
 1924, 3^e ser., XLVII, 771

WAKELEY, G.P.C. Brit. Journ. Surg., Bristol,
 1924-25, XII, 609

eulosis, lymphadenoma, or enteric fever. It is, as a rule, removed by antisyphilitic treatment. When secondarily infected, a gumma may soften and imitate an abscess.¹ The association of a fluctuating swelling in the region of the liver and a raised temperature would render the resemblance to an ordinary hepatic abscess so close that unless the patient was known to have had syphilis there would be no reason to delay surgical treatment. A softened gumma may present anteriorly or may perforate through the ribs and project posteriorly or laterally.

The abdomen of a woman, aged twenty-six years, who had a history of syphilis, was opened and a small gumma excised from the anterior margin of the liver. A hard mass was felt in the right lobe posteriorly and was thought to be a gumma. She was put on iodide of potassium and the right base was aspirated several times, but without success. At the necropsy there was an empyema on the right side and a suppurating gumma, apparently communicating with the empyema, in the posterior part of the right lobe of the liver (Newbolt²).

Tropical hepatitis around a previously quiescent gumma may imitate an abscess, and the true state of affairs be only revealed when caseous material instead of pus is removed at operation.

V. Cases resembling Gall-stones. — ~~Jaundice is not common in tertiary syphilis of the liver, but occasionally~~ the pressure of a gumma or the traction exerted by syphilitic cicatrices in the portal fissure may cause obstructive jaundice. In rare cases this obstructive jaundice is accompanied by attacks of pain resembling biliary colic, but not due to gall-stones. In any case of probable cholelithiasis with well-marked signs of tertiary syphilis iodides should be given before proceeding to operation. The following case recorded by Billings³ bears on this point:

A single man, aged thirty-seven, who had contracted syphilis a year and a half previously, had constant pain in the region of the gall-bladder with attacks of colic followed by jaundice and accompanied by intermittent fever. A tumour was felt in the region of the gall-bladder; Finger operated for cholecystitis and calculi in the gall-bladder and cystic duct, and found multiple gummas; the largest gumma was at the edge of the liver, close to the gall-bladder. The main ducts, however, did not appear to have been pressed upon, so the obstruction must have been in their branches. Similar cases have been described by Riedel,⁴ Parker,⁵ Lilienthal,⁶ Munro,⁷ and Schragar.⁸

VI. Cases resembling Chronic Splenic Anaemia.—In some cases

¹ Barry, C., *Ind. Med. Gaz.*, 1904, xxxix, 298; Thompson, *Lancet*, Lond., 1910, ii, 1415.

² Newbolt. *Med., Surg., and Path. Rep. Roy. Southern Hosp.*, Liverpool, 1901, pp. 143, 248.

³ Billings. *Phila. Med. Journ.*, 1900, vi, 671.

⁴ Riedel. *Milth. a. d. Grenzgeb. d. Med. u. Chir.*, Jena, 1904, xiv, 1.

⁵ Parker, R. *Lancet*, 1899, i, 301.

⁶ Lilienthal. *Ann. Surg.*, 1902, xxxvi, 132.

⁷ Munro. *New York State Journ. of Med.*, 1908, viii, 183.

⁸ Schragar. *Journ. Amer. Med. Assoc.*, Chicago, 1912, lviii, 681.

of syphilitic disease of the liver the spleen is greatly enlarged from lardaceous disease, or in rare instances from gummatous change, while the liver is little, if at all, enlarged. In such cases there may be a considerable resemblance to chronic splenic anaemia which is characterised by anaemia of the chlorotic type, leucopenia or a diminution in the number of leucocytes, and great splenic enlargement. ¹In a case of Coupland's the spleen was removed for supposed splenic anaemia with great apparent benefit; subsequently, when the woman died from haematemesis and ascites, the liver was found to be syphilitic. ²Osler also refers to ~~examples of syphilis imitating chronic splenic anaemia in adults.~~

VII. Cases resembling Hypertrophic Biliary Cirrhosis.—In rare instances syphilis may lead to an enlarged liver with chronic jaundice and splenic enlargement (Hanot³). There may be signs of syphilis elsewhere in the body, the progress of the case is more rapid than in hypertrophic biliary cirrhosis, and the splenic enlargement is not so marked.

A good example of syphilitic disease imitating hypertrophic biliary cirrhosis is given on p. 380. Ferrannini described the case of a woman aged forty-eight years, with jaundice, clay-coloured stools, a large spleen and liver ~~which resembled hypertrophic biliary cirrhosis.~~ At the necropsy the enlargement of the liver and spleen was found to be due to syphilis and the jaundice to a retention cyst in the head of the pancreas compressing the common bile-duct.

Diagnosis.—A history of syphilitic infection, the evidence of syphilitic lesions in some accessible part of the body, such as the skin, tongue, throat, testes, or bones, or a positive ~~result with the Wassermann serum~~ reaction, in an obscure case of hepatic enlargement or tumour, should always be regarded as an indication for antisyphilitic treatment. A patient may deny infection or may be entirely ignorant that he has contracted the disease.

In the following case the patient complained of hepatic pain, had an enlarged liver without jaundice or ascites, and denied syphilitic infection. A labourer aged fifty was under my care in St. George's Hospital in October 1900. For a month he had constant pain in the right hypochondrium, worse at night when lying on the right side and on respiration. Married, no children, but his wife has had four miscarriages. The liver extends below the costal arch in the nipple line and is tender. Spleen not enlarged. Testes not enlarged. There is a rupial scar near the umbilicus. The tongue is greatly deformed and cannot be put out; it is scarred, shews superficial glossitis, and is lobulated, but not ulcerated. The tongue had been sore for six months; this was ascribed by the patient to heavy smoking. On full doses of iodide and mercury the hepatic pain and the condition of the tongue rapidly improved.

¹ Coupland, S. *Brit. Med. Journ.*, 1896, i, 1445.

² Osler, W. *Amer. Journ. Med. Sc.*, 1902, cxxiv, 765.

³ Hanot. *Presse méd.*, 1896, p. 505.

~~Other~~ cases have been described by Osler, Marchand, Chiari, Schmidt

^ | CASTAIGNE

Marchand. München. med. Wchnschr., 1903, L, 463.

Chiari. Prag. med. Wchnschr., 1902,

Schmidt. München. med. Wchnschr., 1911, LVIII, 625.

Castaigne. La clinique, Paris, 1913, VIII, 660 (collects 8 cases).

A man who has contracted syphilis but
as the result of treatment has a persistently
negative Wassermann reaction may be
regarded as cured and free from risk of
hepatitis or other sequelae; whereas a
man with a persistently positive Wassermann
reaction may develop hepatic manifestations.

Hepatic syphilis is probably very commonly overlooked, the disease being regarded as cirrhosis or early new-growth. It is therefore important to bear in mind the possibility of syphilis in all obscure enlargements of the liver and to have the Wassermann test done. Moreover, in doubtful cases invaluable assistance to diagnosis is obtained by watching the effects of a thorough course of mercurials and iodides, or salvarsan. In the early stages of malignant disease it may be quite impossible to come to a correct decision until these have been tried. The differential diagnosis of syphilitic disease of the liver from cirrhosis, chronic peritonitis, malignant disease, etc., has already been referred to under the description of the clinical aspects of syphilitic disease of the liver.

Prognosis.—When properly treated the prognosis is much better than in most of the conditions which resemble it, such as carcinoma, cirrhosis, chronic peritonitis, and perihepatitis. Gummas undergo absorption and the bad effects due to their mechanical effects will disappear. On the other hand, firm cicatrices will, as has already been pointed out, not be affected, and the results of antisymphilitic treatment are therefore disappointing, and, in addition, misleading if absence of a good result be regarded as necessarily eliminating syphilis. The prognosis of syphilitic enlargement, which is often gummatous, is therefore rather better than that of ascites or jaundice thought to depend on syphilitic disease of the liver, since the latter may be due to cicatrices.

Treatment.—Mercurial inunction and iodide of potassium internally should be employed. The three iodides, of potassium, sodium, and ammonium, may be given in combination, or iodide of potassium may be given with spiritus ammoniac aromaticus so as to avoid the depressing effects of potassium. In any event ammonia in some form should be given, as it is said to double the effect of the iodides. The usual course is to begin with fifteen grains of the combined iodides three times daily, which is increased until thirty grains are being taken three times a day. If mercurial inunction be not employed at the same time, liquor hydrargyri perchloridi should be added to each dose of the medicine. The medicine should be taken shortly before meals. If taken after meals, dyspepsia may occur, possibly because some free iodine is liberated by the action of the hydrochloric acid of the gastric juice on the iodides.

The use of iodide of potassium in tertiary syphilis appears to have been first discovered in 1831 by R. Williams, of St. Thomas's Hospital (Sir J. Paget¹); though Wallace, of Dublin, who employed it in 1832 and published his results in the *Lancet* in 1836, is generally credited as the first to use this drug.²

Lancet, 1836, ii, 5.

¹ Sir James Paget. *Address to the Abernethian Society of St. Bartholomew's Hospital*, 1885, p. 19; privately printed. Quoted by Howard Marsh in obituary notice of Sir J. Paget, *St. Barth. Hosp. Rep.*, 1900, xxxvi, 6.

² See Lancereaux. *Syphilis*, 1869, ii, 300. New Sydenham Society.

The good effects of iodides and mercury may not appear for a considerable time. It is essential, therefore, that several weeks' thorough treatment should be insisted upon before it can be concluded that the condition is not syphilitic.

An interesting speculation is opened up by a consideration of the marvellous way in which iodides produce absorption of gummatous material. This action can hardly be considered specific in the strict sense of the term, inasmuch as a similarly marked effect follows its adequate administration in actinomycosis. Possibly iodides prevent further disease of the vessels in the neighbourhood, and this may enable the natural process of absorption to go on unchecked by endarteritis of the neighbouring vessels, while it prevents further syphilitic manifestations. Stockman¹ believes that iodides act by increasing the thyroid secretion, which has a powerful absorptive action. If this be the case, thyroid extract should be given in gummas. Flexner² attributes the absorption of gummas to autolysis or the action of intracellular ferments, and supposes that this ferment action is accelerated by iodides.

Intravenous injections of salvarsan ("606") may be given with due precautions. If the patient is anaemic, iron should be given, iodide of iron being a convenient form. When gummas develop with great rapidity and soon after infection, subcutaneous, or better intramuscular, injection of various mercurial salts may be employed.

Pain due to perihepatitis may be relieved by hot fomentations, by poultices, or by the application of a few leeches over the painful area. The general health should be maintained by a generous diet and by fresh air, preferably that of the sea. Alcohol should be avoided unless there are special reasons for its use. In severe cases with cachexia the medicinal treatment may with advantage be carried out at spas of high elevation, such as Barèges, Cauterets, Bagnères-de-Luchon, or Wildbad-Gastein. Aix-la-Chapelle and Wiesbaden are well adapted for the treatment of visceral syphilis.

Surgical Treatment.—Removal of a gumma may be possible when the anterior margin of the liver is affected, and when the lesion is single and localised, but it is only likely to be performed when an exploratory operation has been undertaken for purposes of diagnosis and when a tumour of uncertain nature is found and can be fairly easily removed. In exceptional instances when a breaking-down gumma is ulcerating through the abdominal wall, scraping out the gummatous sloughs, as in a case described by W. G. Spencer,³ is advisable, inasmuch as toxic absorption is thus prevented.

In a case in which an exploratory operation revealed a very large gumma 4 or 5 inches across, R. Parker⁴ removed some, but not all, of the caseous contents; antisyphilitic remedies were given and the man recovered. In a

¹ Stockman. *Glasgow Hosp. Rep.*, 1899, ii, 69.

² Flexner. *Am. Journ. Med. Sc.*, 1903, cxxvi, 214.

³ Spencer, W. G. *Brit. Med. Journ.*, 1898, ii, 1686; and *Trans. Clin. Soc.*, 1899, xxxii, 46.

⁴ Rushton Parker. *Lancet*, Lond., 1899, i, 301.

remarkable case recorded by Curtis¹ a gumma of the liver firmly adherent to the stomach was removed; the patient left off taking iodides, and three years later a gumma of the liver adherent to the caecum was removed.

Removal of a localised gumma or of a gummatous constriction lobe in cases in which laparotomy has been undertaken to clear up the diagnosis, or under the impression that some other condition was present, is admissible, inasmuch as it may accelerate the cure by antisypilitic treatment. But very thorough antisypilitic treatment should be carried out before an operation is undertaken for removal of a gumma.

In 1907 Cumston² collected 32 cases in which resection of the liver had been performed for gumma. In most cases operation was undertaken under the idea that the hepatic condition was other than a gumma. Steiner³ collected 13 cases in which laparotomy was planned on what turned out to be errors of diagnosis.

Parasyphilitic Affections.—By ~~parasyphilitic~~ or metasypilitic lesions are meant ~~changes which are~~ not pathognomonic of syphilis, but which develop when the soil has been prepared by syphilis; such are tabes dorsalis and general paralysis of the insane. The question of parasyphilitic multilobular cirrhosis occurring in the subjects of congenital syphilis is discussed on p. 381. Pathologists have rightly insisted on the difference between ordinary portal cirrhosis and the specific forms of hepatic fibrosis—namely, unicellular cirrhosis in hereditary syphilis and multiple scarring by cicatrices. This may explain why so little attention has been paid to multilobular cirrhosis as a parasyphilitic sequel. That ~~it not uncommonly happens that~~ a person who has had syphilis becomes the subject of ordinary multilobular cirrhosis is quite natural, since syphilis does not protect in any way against the effects of alcoholism, and, moreover, Bacchus and Venus are frequently worshipped by the same devotees. It is reasonable to believe that parasyphilitic multilobular cirrhosis may occur in adults, but there are considerable difficulties in recognising it or in establishing its existence. Fabris⁴ has recorded a case.

Lardaceous Disease.—With the advance of surgery prolonged supuration has become so infrequent that syphilis is responsible for a much larger proportion of cases of lardaceous disease than formerly. Lardaceous liver is considered on page 433; it need only be stated here that lardaceous change may accompany gummatous and other syphilitic lesions in the liver and that in some instances the lardaceous change is ~~found only~~ around gummas.

Confined to
the immediate
neighbourhood
of

¹ Curtis. *Clin. Journ.*, Lond., 1911, xxxviii, 44.

² Cumston, C. G. *International Clinics*, 1907, 17. s., ii, 124.

³ Steiner. *Thèse de Paris*, 1902, No. 380.

⁴ Fabris. *Arch. per le sc. med.*, Torino, 1908, xxxii, 471.

CONGENITAL SYPHILIS OF THE LIVER

The hepatic lesions due to congenital or hereditary syphilis may conveniently be considered as : (1) Those found in infants at the same time that other manifestations of congenital syphilis are common. (2) Those of delayed or late congenital syphilis. (3) Multilobular cirrhosis in children with a history or signs of former hereditary syphilis ; this constitutes parasymphilitic cirrhosis. The first of these categories is far the most important and is what is ordinarily understood by the liver of congenital syphilis.

History.—Gubler¹ first gave a full account of the lesions of the liver in hereditary or congenital syphilis in 1852. Bamberger, Virchow, and Parrot further described the condition, and in Great Britain Sir S. Wilks recorded a case in 1866. The reader will find references to the history of hereditary hepatic syphilis in Lancereaux's² work. More recently the tertiary effects of congenital syphilis on the liver have been specially described in cases of syphilis hereditaria tardiva.

The Ordinary Hepatic Manifestation of Congenital Syphilis

Incidence.—The liver is affected in a very high proportion of the infants dying with congenital syphilis.

In infants with congenital syphilis the liver has been found to be affected in from 39 per cent (Hofmeister³) to 65 per cent (Feige⁴).

This contrasts with acquired syphilis, in which the liver very frequently escapes. It is generally considered that antenatal syphilis may be either (i) hereditary, and due to the spermatozoon being the carrier of the syphilitic parasite to the ovum, while the mother escapes though rendered immune to further infection ; or (ii) congenital, and due to the syphilitic parasite passing from the mother through the placenta into the umbilical vein of the fetus. The frequency of hepatic lesions in antenatal syphilis is an argument in favour of the view that the infection is maternal, and passes through the placenta into the umbilical vein, damaging the liver, which is the first organ of the fetus with which it comes in contact ; a further argument in favour of this view is that the liver generally contains a larger number of *Treponema pallidum* than the other organs of the infant (McIntosh⁵) ; if the ovum were primarily infected by a syphilitised spermatozoon it is improbable that the embryo would survive ; and further, if it did, the *Treponema pallidum* would reach the liver by the hepatic artery, and the liver, being thus exposed to the same risk of

¹ Gubler. *Mém. Soc. de Biol.*, Paris, 1852, iv, 25.

² Lancereaux. *Syphilis*, 1869, ii, 132, 151. Transl. New Sydenham Soc.

³ Hofmeister. *Dissertation*, Kiel, 1886. Quoted by Quincke in Nothnagel's *Encyclopædia of Practical Medicine*, English translation, p. 745.

⁴ Feige. *Dissertation*, Kiel, 1896. *Ibid.*

⁵ McIntosh. *Journ. Path. and Bacteriol.*, Cambridge, 1909, xiii, 245.

According to Brown the liver in
still born syphilitic infants is
rarely enlarged

Brown, F. J. Brit. med. Journ., 1921, ii, 140

infection as in postnatal syphilis, should be affected in much the same proportion as in the acquired disease. In postnatal syphilis when the disease is conveyed by a wet-nurse, by inoculation, or other means, the lesions are the same as in the acquired disease.

Morbid Anatomy.—*Liver.*—There is very considerable variation in the changes found in the livers of infants dying with congenital syphilis; but the two main points in regard to the morbid anatomy are, (i) that the change tends to be diffuse, and (ii) that it is a secondary syphilitic manifestation. Congenital hepatic syphilis thus differs markedly from the circumscribed lesions of the liver characteristic of the tertiary stage of the acquired disease. The appearance of the liver is by no means constant; sometimes there is little or no manifest change to the naked eye, and microscopic examination alone may make it certain that there is syphilitic infection. The liver is ^{commonly} enlarged, usually retains its shape, and weighs more than natural, being one-twelfth or one-sixteenth instead of one-twenty-fifth of the body-weight at birth. The surface may shew adhesions, due to intrauterine perihepatitis and peritonitis, but except for these adhesions the liver is smooth, and is firmer and more resistant than normal. The healthy colour is altered; occasionally, in the early stages of the disease, it is congested, but usually its tint is lighter than in health; it may be violet, greyish-yellow, and approaching the colour of flint (*foie silex* of Gubler) or yellow. On section it is firmer than natural and resistant, but not to the same extent as in cirrhosis or in congenital obliteration of the bile-ducts. The organ tends to be uniformly affected, but often some parts are more affected than others, so that a mottled appearance is presented. The alteration in colour is the same as described above, but the mottling may be more marked; areas presenting the yellow change may alternate with parts preserving the more or less healthy red colour, and the appearance may suggest primary sarcoma. In other instances the glistening, semi-translucent aspect suggests lardaceous change.

On carefully examining the cut surface small grey spots like grains of semolina are generally visible; they are small granulomas or syphilomas and composed of small round cells; in some instances the central portions of these granulomas shew caseation and may then be spoken of as miliary gummas. The left lobe is said to be more often affected with these syphilomas. To the naked eye these look like small miliary tubercles, and microscopically they so far resemble them in being localised collections of small round cells. Tuberculosis may indeed be associated with intercellular cirrhosis, and the distinction between these small syphilomas and miliary tubercles depends on the presence of the corresponding parasite. In rare instances caseous gummas have been found in infants and even in stillborn children and premature fetuses.

Canton¹ figured multiple hepatic gummas in a child of seven weeks, and T. Barlow² described "receding gummata" in a child twelve weeks old.

¹ Canton E. *Trans. Path. Soc.*, 1861-2, xiii, 113.

² Barlow, T. *Ibid.*, 1877, xxvii, 202.

Bittner¹ recorded gummas in the liver of a stillborn child and in a six months fetus. Other cases are given by Lancereaux² and by Hutinel and Hudelo.³

The *microscopic appearances* vary greatly according to the duration and virulence of the infection. In the earliest stage there is capillary congestion with perivascular small-celled infiltration, which subsequently becomes diffuse. These newly formed cells are the outcome of proliferation of (a) the pre-existing connective-tissue cells of the organ; (b) of the endothelium of the capillaries and lymphatics inside the hepatic lobules, whilst Kupffer's star-like cells, which are intimately connected with the en-

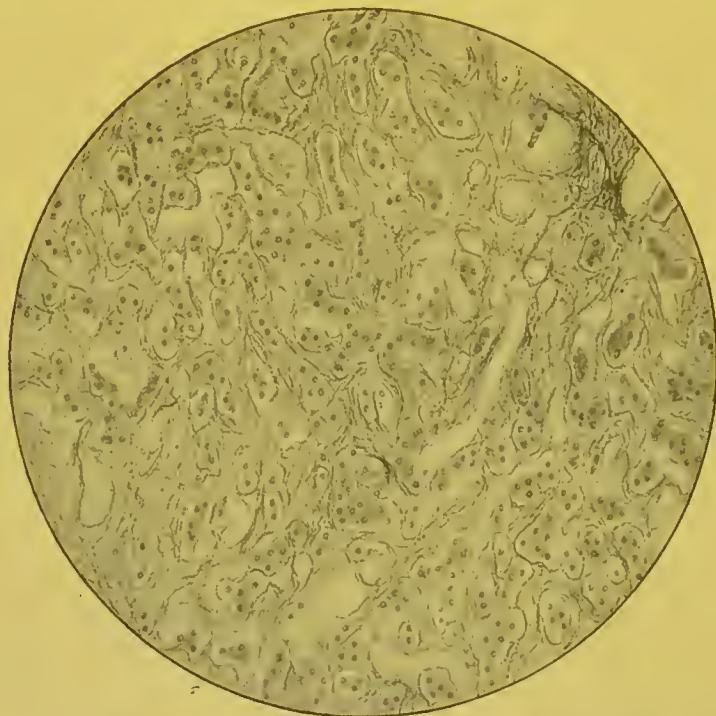


FIG. 46.—Microscopic appearances in intercellular cirrhosis. There is delicate connective tissue between the small groups of liver cells.

dothelial lining of these vessels, share in this process. This diffuse infiltration closely resembles an infiltrating sarcoma, and naturally, since proliferation of the connective tissues during fetal life or soon after birth leads to a formation which is structurally much the same as that of a sarcoma. It is extremely probable that some cases described as diffuse sarcoma in early life were in reality examples of the hepatic lesion of hereditary syphilis. By appropriate staining methods numbers of *Treponema pallidum* (*Spirochaeta pallida*) can be seen (*vide* Fig. 46) in the connective tissue between the liver cells and the sinusoids. Erythroblastic foci are present (Erdmann).

At a rather later stage the fibroblasts separate the individual liver

¹ Bittner. *Prag. med. Wchnschr.*, 1877, xviii, 581.

² Lancereaux. *A Treatise on Syphilis*, ii, 152. Transl. New. Syd. Soc., 1869.

³ Hutinel et Hudelo. *Arch. de méd. expér. et d'anat. path.*, Paris, 1890, x, 509.

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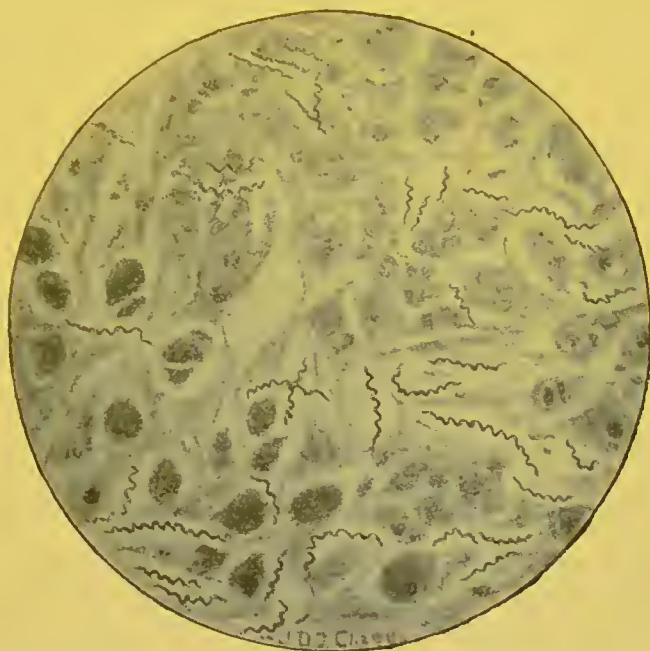
kind of
lymphatic
infiltration
or

ERDMANN. Deutsches Arch. f. klin. Med., Leipz., 1902, Lxxiv, 458.

, which may closely
resemble sarcoma, | ^

cells from each other. There is thus a pericellular, unicellular, or intercellular cirrhosis. This appearance is occasionally seen in the secondary stage of syphilis, and locally in some cases of ordinary portal cirrhosis. Sometimes the microscopic appearances of intercellular cirrhosis at this stage are like those of an infiltrating carcinoma.

As time goes on the organisation of young connective tissue may ~~advance and~~ lead to well-formed fibrous tissue. The chronic nature of the inflammation, if allowed to run its course, is often well shewn by the presence of both well-formed fibrous tissue and recent inflammatory or granulation tissue in the same specimen. The fibrous tissue of Glisson's



McNee will
provide
photographs

FIG. 47.—Section of liver in congenital syphilis shewing *Treponema pallidum* (E. O. Jordan).

capsule in the portal canals is also increased in amount. In places there may be collections of small round cells—syphilomas—or, as they are often called, miliary gummas, though the word “gumma” should be reserved for the further stage of necrosis and caseation. These small syphilomas may be found in association with early intercellular infiltration, or later, when there is well-formed fibrous tissue.

The hepatic lesions which can be regarded as a remote result of congenital syphilis will be referred to again under the heading of “Delayed Congenital Syphilis,” but here it may be pointed out that although ordinary cirrhosis may very probably supervene in a liver recovering from intercellular cirrhosis, it does not appear reasonable to imagine that intercellular cirrhosis can be directly transformed into multilobular or unilobular cirrhosis. Extensive fibrosis of the liver producing a tumour-like mass is sometimes seen as the result of congenital syphilis. Some

with

cases of the kind have been described as fibroma of the liver. Marchand¹ has insisted on the syphilitic nature of these cases.

As an example of very extensive fibrosis Morley Fletcher's² case of a child aged eight weeks may be referred to. The mother had had seven other healthy children and one stillborn infant, but no other evidence of syphilis was forthcoming. The liver was much enlarged and easily felt. There was no jaundice or ascites. The liver (28 oz.) microscopically shewed great fibrosis, the fibrous tissue being well formed; in addition, there were areas with much small-celled infiltration. The hepatic cells were greatly atrophied, compressed, and in many places formed columns resembling pseudobile canaliculi (*vide* Fig. 48); there was a considerable amount of extravasation of red corpuscles. The spleen was not enlarged. The right suprarenal was enlarged to the size of its corresponding kidney and there were fibrosis and extravasation into the medulla. In this case, as in those recorded by Marchand, some doubt as to the existence of syphilis might arise.

The liver cells are atrophied, compressed, and may shew granular and degenerative changes. Fatty change is not frequent, and when present is usually quite sporadic and localised. As the result of necrosis they may disappear from considerable areas, their place being taken by organising granulation-tissue. The liver cells may be so compressed that they closely resemble newly formed bile-ducts. In rare instances the liver cells shew great enlargement and contain many nuclei (Binder,³ Oppenheimer,⁴ Ménétrier and Rubens-Duval⁵). The giant or plasmodial liver cells have been thought by Binder to be due to fusion of hepatic cells, and by the other observers mentioned as the result of nuclear division without cell-division, the process being due to the action of the syphilitic toxin.

The hepatic artery is normal and is free from endarteritis, a change which would naturally be expected if the syphilitic virus reached the liver from the general circulation. In exceptional instances, however, endarteritis and periarteritis and phlebitis are present (Oberndorfer⁶). There is an increase in the amount of fibrous tissue and in exceptional instances marked inflammatory changes around the bile-ducts and portal vein in the portal spaces. Endophlebitis of the branches of the hepatic veins sometimes occurs, and if allowed to progress, may eventually lead to stenosis of the orifice of these veins (*vide* p. 50).

The variations met with in the liver in congenital syphilis depend on the severity of the infection and its duration. The following conditions may be recognised:

I. The commonest change is a diffuse embryonic infiltration which develops into young connective-tissue cells separating the individual liver cells; this is intercellular, unicellular, or pericellular cirrhosis.

¹ Marchand. *Centralbl. f. allg. Path.*, 1896, vii, 273.

² Morley Fletcher, H. *Trans. Path. Soc.*, Lond., 1899, 1, 138.

³ Binder. *Virchows Arch.*, 1904, clxxvii, 44.

⁴ Oppenheimer. *Ibid.*, 1905, elxxxii, 237.

⁵ Ménétrier et Rubens-Duval. *Arch. de méd. expér. et d'anat. path.*, Paris, 1907, xix,

⁶ Oberndorfer. *Centralbl. f. allg. Path. u. path. Anat.*, 1900, v, 145.

II. The previous condition may be combined with small collections of round cells or miliary gummas.

III. Further organisation of the intercellular infiltration leads to wide-spread or local areas of fibrosis.

IV. Occasionally well-formed caseous gummas like those seen in adults are present.

V. A combination of gummas with fibrosis (gummatous hepatitis) not affecting the whole organ, but forming circumscribed areas which may imitate a tumour.

The diffuse intercellular cirrhosis is, like the lesions of secondary

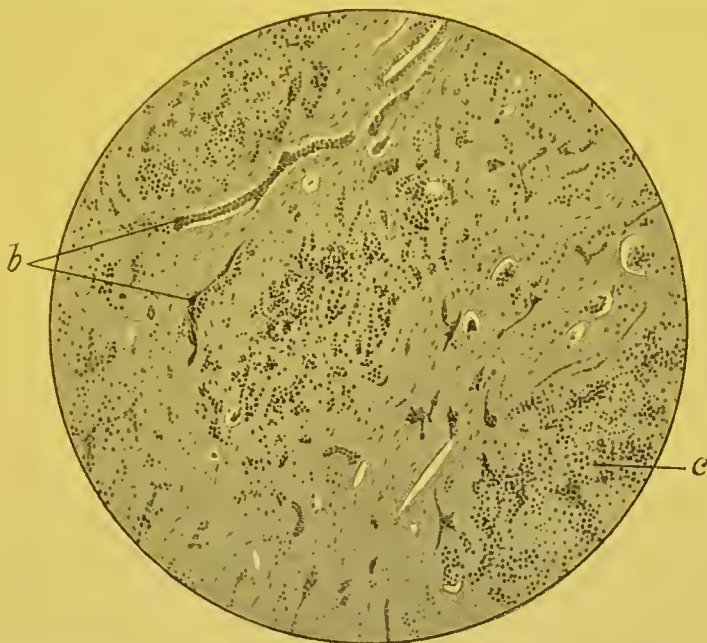


FIG. 48.—Microscopic section from a case of congenital syphilis. Shews extensive fibrosis, areas of small-celled infiltration (c), compressed liver cells, and columns of cells resembling small bile-ducts (b). (Drawing kindly lent by Dr. H. Morley Fletcher.)

syphilis elsewhere, essentially curable if treated with mercury. It may, however, pass into the tertiary lesions, and gummas, cicatrices, and lardaceous change may develop (*vide* p. 378).

The *spleen* is generally enlarged; according to Marfan the spleen of stillborn syphilitic infants weighs four times the normal. From fibrosis it becomes firmer than natural. Lardaceous disease may be seen in older children. Gummas are extremely rare; Still¹ could only find two cases in infants. There may be adhesions between the capsule and adjacent parts. Microscopically there is fibrosis.

The *kidneys* may also present interstitial fibrosis. This is of interest in connexion with Payne's² view that granular kidneys in young children depend on hereditary syphilis. There may be diffuse small-celled infiltration

¹ Still. *Trans. Path. Soc., Lond.*, 1897, xlviii, 205.

² Payne, J. F. *Ibid.*, 1900, li, 364.

in the pancreas and testes, and changes in the lungs are comparatively frequent. The suprarenals are enlarged, and may shew small-celled infiltration, haemorrhage, or fatty change.

Clinical Features.—When the infection is advanced, the child may be stillborn or die a few days after birth. In many cases the child is healthy when born and subsequently develops evidences of congenital syphilis. For some unknown reason girls are more prone to congenital syphilis than boys. As a general rule, signs pointing definitely to the liver, such as jaundice and ascites, are absent, and it is only on examination that the liver and spleen are found to be enlarged. The clinical features may be summarised thus: the well-known manifestations of hereditary syphilis are present, and, in addition, there is enlargement of the spleen and liver.

The enlarged liver may reach down to the iliac crest; Carpenter¹ found the liver enlarged in 47 per cent of the cases of inherited syphilis under six months of age; and in 148 cases it was palpably so in 48 (Hochsinger²). It must be borne in mind that in young children the liver normally projects further down than in adults; this is not merely due to the relatively larger size of the organ in children, but also to the more horizontal position of the ribs, which leaves the organ less covered. Hence slight apparent enlargement is not of importance in the absence of other evidence. The degree of hepatic enlargement corresponds with that of the other manifestations of the disease, and may therefore be taken as an index of the severity of the infection. The liver is firm, tender, and somewhat resistant. In very rare cases there is a localised tumour formation which is readily felt during life (*vide* p. 373).

In a child three months old, icterus, ascites, and cerebral symptoms were associated with a gummatous projection from the under surface of the right lobe of the liver (Cohn³).

The spleen is commonly enlarged in hereditary syphilis. This was pointed out by Gee⁴ in 1867, who found clinical evidence of splenic enlargement in one-fourth of his cases.

More recently the incidence of splenic enlargement in congenital syphilis has been estimated at 45 per cent by Still,⁵ 50 per cent by Marfan,⁶ and at 63 by Coutts.⁷

Jaundice occasionally occurs, and is probably not so extremely rare as is often stated. It may be due to various factors. It may possibly depend on pressure of enlarged glands in the portal fissure on the ducts, or on pressure exerted by masses of syphilitic granulation-tissue, but is more probably due to inflammatory changes in the small bile-ducts which

¹ Carpenter. *Syphilis in Children*, p. 53, 1901.

² Hochsinger. *Wien. med. Wchnschr.*, 1896, xlv, 345.

³ Cohn, M. *Virchows Arch.*, 1896, cxlvi, 468.

⁴ Gee, S. *Brit. Med. Journ.*, 1867, i, 435.

⁵ Still. *Practitioner*, 1904, lxxiii, 101.

⁶ Marfan. *Rev. mens. des maladies de l'enfance*, 1903, xxi, 211.

⁷ Coutts. *Brit. Med. Journ.*, 1896, i, 1026.

Congenital haemolytic jaundice
has been recorded in congenital
syphilis (FOURNIER and JOLTRAIN).

FOURNIER ~~et~~ JOLTRAIN. Bull. et mêm. Soc. m.
des hôp. de Paris, 191
3.2., XXXV, 487.

form part of the diffuse unicellular hepatitis. In the latter case it is much the same as the jaundice occasionally seen in the secondary stage of acquired syphilis. I have seen death from haematemesis in jaundice due to congenital syphilis. Secondary infection may cause jaundice in congenital syphilis; it may be due to *B. coli* or *B. proteus* (Milon,¹ Bar and Rénon²). The micro-organisms may enter through the umbilical vein and find a suitable nidus in the liver, the resistance of which has been reduced by the syphilitic lesion. The development of jaundice is thus comparable to icterus gravis supervening in ordinary cirrhosis. The aspect of the case may then be one of multiple haemorrhages and resemble the acute umbilical infections in the newly born. Perry and Shaw³ refer to a case of this kind in an infant two weeks old. λ

When jaundice is met with in congenital syphilis, it is usually present at birth, but it may not come on until some weeks later. In rare cases the jaundice may pass away and return again.

Still⁴ refers to a boy who was jaundiced for the first six weeks of life; he then recovered and appeared perfectly healthy until the age of two years and three months, when he again became attacked by jaundice, which, after lasting some weeks, proved fatal. Microscopically the liver shewed intercellular cirrhosis.

Ascites is very rare; it may be due to concomitant peritonitis and perihepatitis, which are not very rare in severe cases, or possibly to the pressure of enlarged glands in the portal fissure. In intrauterine life hepatic syphilis may so interfere with the circulation through the umbilical vein as to produce hydramnios, and a number of premature deaths are thus accounted for. But in infants which survive there is not sufficient phlebitis of the portal vein to produce ascites. The abdomen is somewhat distended, partly from enlargement of the liver and spleen, and partly from tympanites. Prominence of the subcutaneous abdominal veins is ^{or} sometimes ~~noticeable~~. The usual symptoms and signs of congenital syphilis, such as debility, wasting, the cutaneous, mucous, and bony lesions, anaemia, and in some cases multiple haemorrhages, vomiting, and diarrhoea, are present. λ /prominent

Diagnosis.—This is usually very much easier than in acquired syphilis of the liver in adults, inasmuch as there are usually well-marked signs of syphilis elsewhere in the infant. In the absence of these signs other causes for enlargement of the liver and spleen, such as rickets, tuberculosis, gastro-intestinal infection, must be considered and as far as possible eliminated. Caseous tubercle in the liver in young infants has imitated syphilitic disease almost exactly (Hochsinger⁵). In cases in which there is jaundice from birth without any manifest signs of syphilis, simple jaundice and congenital obliteration of the ducts must be

¹ Milon. *Thèse de Paris*, 1897, No. 434.

² Bar et Rénon. *Compt. rend. Soc. Biol.*, Paris, 1895, xlvii, 379. } l.

³ Perry and Shaw. *Guy's Hosp. Rep.*, 1893, 1, 226.

⁴ Still. *Clin. Journ.*, 1901, xvii, 322.

⁵ Hochsinger. *Wien. med. Bl.*, 1894, xvii 255.

borne in mind. A positive Wassermann reaction practically clinches the diagnosis.

Prognosis.—The prognosis depends on the general state of nutrition and on efficient and prompt antisypilitic treatment. If the liver and spleen are greatly enlarged, the prognosis is grave. Visceral enlargement may be regarded as an index of the severity of the infection. Haemorrhages are of bad omen, and cases with jaundice usually do badly.

Treatment.—The treatment is that of congenital syphilis; mercury may be given by inunction or by the mouth. Hydrargyrum cum cretâ may be given in the form of a powder: to a child under two months $\frac{1}{2}$ grain twice a day; after that age the dose is increased to one grain. Liquor hydrargyri perchloridi may be given instead or the French preparation of Liqueur de Van Swieten in doses of 10 minims daily for a child of one month old, increasing the doses by 5 or 10 minims every month or so. A more satisfactory method, both because it acts more rapidly and is less likely to lead to salivation, is mercurial inunction. Mercurial ointment is rubbed on with flannel, into the axillae, over the liver, and over the spleen, a fresh situation being selected daily. To begin with, about 15 grains of the ointment should be used every day. The mercurial treatment should be carried out daily for three months, and then relaxed gradually; in the fourth month the treatment being intermitted for a week at a time, and in the fifth month for two weeks. In the second year of treatment mercurial inunction should be performed during one month out of three, and small doses of iodide of potassium given. In the third year the dose of the iodide may be increased, and in the fourth year the mercurial treatment may be dropped, while the iodide is continued. In this way the appearance of tertiary manifestations should be prevented. In order to prevent both abortion and syphilitic infection of the fetus a pregnant woman known to be the subject of syphilis should go through a course of antisypilitic treatment.

Salvarsan has been injected into syphilitic infants; but in sucklings it is safer to inject the mother first, as some therapeutic substance is evidently contained in the milk; if no improvement occurs or if it is slight, the infant can then be injected with less risk (McIntosh and Fildes¹).

The Hepatic Manifestation of Delayed Congenital Syphilis

Synonym: Late ^{congenital} Hereditary Syphilis.

Description.—The changes in the liver are the same as in the tertiary stage of the acquired disease, but they occur in the subjects of ^{congenital} undoubted ~~hereditary~~ syphilis.

History.—Probably the first case was recorded in 1863 by S. Wilks,² in a girl aged twelve years whose mother had had secondary syphilis.

¹ McIntosh and Fildes. *Syphilis from the Modern Standpoint*, 1911, p. 189, Lond.

² Wilks, S. *Guy's Hosp. Rep.*, 1863, ix, 24.

Injection of neo-salvarsan into the veins of the scalp is said
to be more effective than mercurial treatment (Fondlay and Robertson)

Fondlay and Robertson Quart. Journ. Med., Oxford 1914-15, viii, 175

Chronic exudative peritonitis
may be due to extension from
the liver and spleen (ACUÑA and
CABAUBON).

ACUÑA, M. et CABAUBON, A. Arch. Méd. des enf., Paris
1922, XXV, 259.

The child's liver was much deformed and contained gummas and numerous cicatrices.

H. Morris' ¹ case was one of the earlier examples of tardive hereditary syphilis. The patient was a girl aged twenty years with a family history of syphilis and a personal history of interstitial keratitis. The liver was noticed to be enlarged at eighteen, and ascites appeared in the course of the next year. At the necropsy the liver, which weighed 39 ounces, was fissured, puckered, lardaceous, and contained gummas; the kidneys and spleen were also lardaceous.

Incidence.—A considerable number of cases, probably about 70, have been recorded. In 1886 Fournier ² collected 25, and in 1890 Hudelo ³ referred to 49 cases. The liver is affected in about a third of the cases; out of 132 cases of delayed inherited syphilis the bones were affected in 39 per cent, the liver coming next in 34 per cent (Forbes ⁴).

The hepatic lesions are tertiary in character and are the same as those seen in the acquired disease. In order to be sure that the case is one of delayed congenital syphilis there must be some other evidence of the congenital affection, such as interstitial keratitis, otherwise the disease might have been acquired in early life; for example, from a wet-nurse.

Morbid Anatomy.—The liver is nearly always enlarged and is changed in much the same way as in the tertiary stage of the acquired disease. It may be very greatly deformed and cut up into numerous lobes; it is highly probable that some of the recorded anatomical abnormalities of multiple lobulation (as many as 16 lobes have been described) can be thus explained. The lesions are gummas, cicatrices; fibrosis, intercellular cirrhosis, and ~~lardaceous~~ change in varying degrees and combinations. It is well to remember that, as in early congenital syphilis, the naked-eye appearance of the liver may suggest malignant disease; this was the first naked-eye diagnosis in a boy aged fifteen years with delayed hereditary hepatic syphilis described by H. W. G. Mackenzie. ⁵ In order to exclude caseous tubercles, Devie and Froment ⁶ consider a microscopic examination necessary; of 53 recorded cases of late hereditary syphilis these authors consider 25 probable and only 6 certain examples. Perihepatitis is common and may be the means by which gummatous inflammation spreads to the abdominal wall. The other organs may shew syphilitic lesions and advanced ~~lardaceous~~ disease.

Clinical Features.—The subjects of delayed hereditary syphilis of the liver usually display copious signs of syphilitic infection in the bones, sense organs, or in the existence of widespread lardaceous disease. They

¹ Morris, H. *Trans. Path. Soc.*, Lond., 1879, xxi, 214.

² Fournier. *La Syphilis héréditaire tardive*, 1886.

³ Hudelo. *Thèse de Paris*, 1890. Quoted by Chauffard, *Traité de Médecine* (Bouchard, Brissaud), v, 265.

⁴ Forbes. *St. Barth. Hosp. Rep.*, 1902, xxxviii, 37.

⁵ Mackenzie, H. W. G. *Trans. Path. Soc.*, Lond., 1892, xliii, 84.

⁶ Devie et Froment. *Ann. de dermat. et de syph.*, Paris, 1906, 4. s., vii, 97.

amyloid

congenital

amyloid

are ill developed, look much less than their years, and are examples of what has been called infantilism. The usual age is between ten and twenty years. The liver is nearly always enlarged and may even appear as a tumour.

In Post's¹ case, a boy aged twenty-two years, the subject of late hereditary syphilis, there were gummas in various bones, in the pancreas, and in the liver. A gumma in the liver had become adherent to and invaded the abdominal wall, giving rise during life to a very definite tumour. Besides gummas the liver shewed very diffuse fibrosis. The patient died from an acute streptococcic infection. Bristowe's² patient, a boy aged fifteen years, had a tumour of uncertain nature connected with the liver which yielded nothing on aspiration. The temperature was hectic. On antisypilitic treatment the signs and symptoms all disappeared.



FIG. 49.—Clubbing of the fingers in a case of late hereditary syphilis. (Photographed by Dr. H. G. Drake Brockman.)

When The spleen is enlarged either from lardaceous change or independently, as in the following case,³ which imitated hypertrophic biliary cirrhosis.

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& jaundice
the condition
may*
A boy aged seventeen years had chronic jaundice of some years' duration, subcutaneous gummas, periostitis, enlarged spleen and liver, and clubbed fingers. He was the subject of congenital syphilis. Death was due to erysipelas complicated by pericarditis and peritonitis. The liver weighed 5 pounds, the right lobe was much scarred by gummas and was small, a fibrous mass compressed the common hepatic duct just at its commencement and obstructed the entrance of the two hepatic ducts into it. The spleen weighed 45 ounces. None of the organs were lardaceous.

There may be oedema of the feet, evidence of lardaceous disease of the kidneys, and eventually uraemia. Jaundice is rare, but ascites is very common. Jaundice and ascites may be due to pressure exerted by gummas or cicatrices in the portal fissure, while ascites may be part

¹ Post. *Boston City Hosp. Rep.*, 1898, 233.

² Bristowe. *Brit. Med. Journ.*, 1886, i, 878.

³ Lazarus-Barlow, W. S. *Trans. Path. Soc.*, 1899, 1, 158.

Bamberger³ reported 2 ~~cases~~^{brothers} with the clinical features of Biliary Atresia probably due to syphilis

3 Bamberger. Journ. Amer. Med. Assoc., Chicago, 1924, LXXV, 743

and Banti's disease (oste

Osler. Proc. Roy. Soc. Med., 1913, vii, (Med. Sect.) 1.

of the general dropsy of lardaceous kidney disease. There may be fever as in the acquired form (*vide* p. 364). In some instances there is widespread arteriosclerosis, with so much endarteritis obliterans that the pulses in the limbs may be absent. Death may be due to secondary infections, such as erysipelas, ~~or be due to~~ uraemia, cardiac failure, ~~or~~ asthenia, ~~or haemorrhage from an~~ *oesophageal varix (oslov)*

In a well marked case of delayed hereditary syphilis, with hepatic gummas and lardaceous disease, in a girl aged twenty years in St. George's Hospital death was due to terminal peritonitis.

Diagnosis rests on the evidence of congenital syphilis, namely, interstitial keratitis, Hutchinson's teeth, deafness, and infantilism, together with hepatic enlargement. If evidences of syphilis common to the congenital and the acquired forms, such as gummas and lardaceous disease, are present and none of the stigmata of the congenital form are obvious, the infection may have been acquired in early life. But from the point of view of treatment an accurate distinction between them is unnecessary. The following case illustrates the difficulties which may arise in classification :

There was late hereditary syphilis, but the hepatic lesions were of the secondary and not of the tertiary stage. Clinically the hepatic enlargement must have appeared to have been undoubtedly of a tertiary nature. In a case of the congenital syphilitic disease with Parrot's pseudo-paralysis, deafness, and other stigmata in a girl aged twenty-one years, recorded by Touche,¹ the liver, which weighed 104 ounces, only shewed intercellular cirrhosis, although gummas and tertiary lesions were present in the bones.

When, as is often the case, the most prominent features are those of enlarged liver, ascites, and lardaceous disease, the diagnosis turns on evidence of past syphilis ; failing this and any other cause for lardaceous disease, such as prolonged suppuration, late hereditary syphilis should be thought of.

The *differential diagnosis* must be made from hydatid cyst and possibly from sarcoma, or, if there be fever, from abscess ; from cirrhosis, ~~and~~ tuberculous peritonitis, when ascites is the predominating feature ; and from chronic nephritis, when dropsy and albuminuria are due to lardaceous disease.

Prognosis ~~in this stage~~ is not so favourable as in acquired tertiary syphilis of the liver ; the effects of the poison are more widespread, and the frequency with which extensive lardaceous disease is present makes the outlook very grave.

The *treatment* is that of acquired syphilis in its tertiary stage (*vide* p. 367).

Parasyphilitic Multilobular Cirrhosis

Multilobular cirrhosis in young subjects with congenital syphilis is of considerable interest. The diffuse intercellular cirrhosis of infants

¹ Touche. *Bull. Soc. Anat.*, Paris, 1900, lxxv, 852.

suffering from congenital syphilis is, like the lesions of the secondary stage of the acquired disease, a curable condition. Microscopic examination of the livers of children formerly affected with hereditary syphilis may not shew any disease. On the other hand, every now and again the liver of a child with stigmata of congenital syphilis shews ordinary cirrhosis. The arrangement of the two lesions is so dissimilar that intercellular cirrhosis cannot be thought to be transformed into multilobular cirrhosis; it would rather lead to diffuse fibrosis or gummatous change. It seems probable that the intercellular cirrhosis undergoes absorption, but that some vulnerability or diminished resistance of the liver is left behind. If causes that tend to produce ordinary cirrhosis then arise, this change will be readily produced. In other words, the multilobular cirrhosis is a parasymphilitic lesion, and is comparable to general paralysis of the insane, ~~in that, though not syphilitic, it is~~ favoured by syphilisation of the soil (cf. Payne¹).

Sometimes multilobular cirrhosis due to its ordinary causes may supervene in a liver in which intercellular cirrhosis still exists. This would account for some cases of very extensive fibrosis, chiefly of the multilobular type, but in which there are in addition areas of fibrosis suggesting that intercellular cirrhosis has gone on to organisation. Occasionally in multilobular cirrhosis in the subjects of congenital syphilis there is early lardaceous change in the organ.

The *clinical features* are much the same as those of portal cirrhosis in children. Parkes Weber² describes syphilitic splenomegaly with recurring attacks of jaundice and portal cirrhosis. What proportion of the cases of advanced portal cirrhosis of the liver in children have a syphilitic substratum it is difficult to determine; but the reported cases shew that direct evidence of syphilis is often absent. The following case illustrates the marked cirrhosis that may develop in the wake of congenital syphilis and the importance of a microscopic examination in distinguishing this condition from late hereditary syphilis:

A boy aged thirteen years, who had never taken alcohol, was the third child of his mother, who had four miscarriages after his birth. In May 1898 the abdomen enlarged, he became languid, and in August he became short of breath, and haematemesis and melaena occurred. On admission to St. George's Hospital the liver was much enlarged, reaching three finger-breadths below the costal arch, and dilated veins were present on the abdominal wall. He was twice tapped for ascites; death occurred three weeks after the last tapping. There was no oedema of the feet or albuminuria. At the necropsy the liver (42 oz.) was enlarged, granular on the surface, and on section shewed white areas suggesting gummatous infiltration. These were especially well marked around the hepatic veins, and by narrowing them had induced thrombosis. Microscopically, however, these areas did not shew any caseation, but a high degree of multilobular and intercellular fibrosis. There was no lardaceous change. The spleen (16 oz.) was enlarged, and contained a large

¹ Payne. *Trans. Path. Soc.*, Lond., 1900, li, 366.

² Weber, F. P. *Brit. Journ. Child. Dis.*, Lond., 1911, viii, 97.

On the other hand

or a lesion due to parenchymatous syphilis

Transfer
to next
page

In 6 London hospitals
there were 11 cases of
hepatic actinomycosis
in the years 1902-12

Proc. Roy. Soc. Med., 1913, vi (Surg. Sect.), 15

fibrous area. The oesophageal veins were dilated. The testes and kidneys were healthy. The liver is in St. George's Hospital Museum, Series ix, 174ⁱ, and was described by Dr. Lazarus-Barlow.¹

Diagnosis.—It may be difficult to differentiate between these cases of cirrhosis in individuals with other manifest signs of congenital syphilis, on the one hand, and cases of late hereditary syphilis with hepatic lesions and ascites, on the other hand. In the latter there may be excessive lardaceous disease, as shewn by albuminuria. Iodide of potassium and mercury should be tried; improvement will point to hepatic gummas due to late hereditary syphilis, and the treatment must then be pushed.

The prognosis of these cases is very bad.

The treatment is that of ordinary cirrhosis, viz. milk diet, no alcohol or irritating food. Constipation should be prevented by seeing that plenty of water is taken, and if necessary by calomel and saline purges. Flatulence and excessive intestinal fermentation and putrefaction should be prevented by relieving constipation or by minute doses of calomel ($\frac{1}{20}$ to $\frac{1}{40}$ grain) or of perchloride of mercury. Mercury and the iodides of potassium, sodium, and ammonium should be given to prevent if possible any further progress in the disease. But as the lesion is parasymphilitic rather than syphilitic, iodides cannot be expected to remove the fibrosis. Weber advises caution in antisymphilitic treatment and recommends iodide of iron. In other respects the treatment is on the same lines as in portal cirrhosis.

ACTINOMYCOSIS

Incidence.—Actinomycosis (*ἀκτίς*, a ray, *μύκης*, a fungus) is rather rare in Great Britain and America; less so in Germany, Austria, Russia, and Norway. In France its reputed rarity appears to be due to the disease having escaped recognition; Duvau² has collected 146 cases observed in that country. Acland³ collected 109 cases recorded in Great Britain. In 1902 Erving⁴ collected 100 cases in America. In 1094 cases of human actinomycosis collected by Ruhrah,⁵ 604, or 56 per cent, were in the head and neck, 223, or 20 per cent, in the digestive tract, 164, or 15 per cent, in the respiratory tract, 26, or 2 per cent, in the skin; and 63, or 6 per cent, were doubtful.

Etiology.—Actinomycosis is about three times commoner in men than in women.

¹ Lazarus-Barlow, W.S. *Trans. Path. Soc.*, 1899, 1, 146.

² Duvau. *Thèse de Lyon*, 1902, No. 92.

³ Acland. *System of Medicine* (Allbutt and Rolleston), 1907, ii, part i, 332.

⁴ Erving, W. *Johns Hopkins Hosp. Bull.*, 1902, xiii, 261.

⁵ Ruhrah. *Ann. Surg.*, 1899, xxx, 417.

On the basis of 405 cases Leith¹ estimated that 73 per cent were males and 27 per cent females.

It is most frequent between the ages of twenty-five and forty-five years.

It is generally stated that the infection is conveyed into the body by grain and other vegetable material. Homer Wright² considers this erroneous, and believes that the specific micro-organism—*Actinomyces bovis*—is a normal inhabitant of the alimentary canal.

Actinomycosis of the liver is rare. In 1903 Auvray³ was only able to collect 31 published cases, but in Acland's 109 cases, collected from Great Britain only, the liver was invaded in 32.

Method of Origin.—Actinomycosis of the liver must be either metastatic, the infection being conveyed by the blood-stream from a mucous or cutaneous surface, or due to the direct spread of the disease from a focus in the neighbourhood. In the majority of instances the primary focus is in the alimentary canal, from which infection may spread either by the blood-stream or by continuity. In the latter event there may be a mass of inflammatory tissue extending between the affected part of the bowel, usually near the caecum, and the liver. In rare instances there is a direct spread of the actinomycotic growth from the skin of the abdominal wall or from the base of the right lung into the liver. In exceptional instances the infection has entered through the female genital tract. (Grainger Stewart and Muir,⁴ and a case in St. George's Hospital, *vide* p. 386.) The primary focus, usually in the intestine, may heal so that it is very difficult or impossible to determine its situation. Such cases, of which Aribaud collected seven, have been called primary actinomycosis of the liver.

In 30 cases of hepatic actinomycosis collected by Aribaud⁵ the growth was derived from the intestinal tract in 20. In 12 of these it spread by metastases and in the remaining 8 by direct extension.

Actinomycosis in the head and neck very seldom leads to infection of the liver.

Moodie⁶ recorded a case in which a small circumscribed primary actinomycotic tumour of the upper jaw gave rise to a large actinomycoma of the liver.

Actinomyces or the ray fungus belongs to the streptothrix group and presents pleomorphic characters. It may appear as filaments, as cocci, or clubs. The clubs are often absent in human actinomycosis. For a description of the parasite the reader should refer to bacteriological text-

¹ Leith. *Edin. Hosp. Rep.*, 1894, ii, 121.

13 1036

² Wright, J. H. *System of Medicine* (Osler and M'Crae), 1902, i, 285.

³ Auvray. *Rev. de chir.*, Paris, 1903, xxiii, 1.

⁴ Grainger Stewart and Muir. *Edin. Hosp. Rep.*, 1893, i, 96.

⁵ Aribaud. *Thèse de Lyon*, 1897.

⁶ Moodie, E. L. *Journ. Path. and Bacteriol.*, 1902, viii, 239.

Take in place
from previous page.

Kellock believes that Actinomyces fungus
works its way up the bile ducts and that
infection of the liver is continuous with that
of the appendix.

Wright separates Actinomyces
from Septicæmia

books. Cases of infection with branched filamentous organisms somewhat resembling, but not, *Actinomyces bovis*, and sometimes described as pseudo-actinomyces, are now called nocardiosis (Wright).

Morbid Anatomy.—The liver is enlarged and shows adhesions on the surface. The morbid condition varies very considerably. The actinomycotic abscess has a characteristic honeycombed aspect and has been compared to a sponge soaked in pus. The alveolar appearance is due to the coalescence of a number of small abscesses. The suppurative process spreads by continuity, and is accordingly more or less localised; but sometimes small abscesses are seen away from the main collection, or there may be multiple abscesses, like those seen in pyæmia.¹ The individual abscesses vary in size from a pin's head to that of a walnut.

Inflammation of the capsule of the liver and adhesions to adjacent organs are very common. When situated anteriorly, the actinomycotic lesion readily extends, after adhesions have been formed, to the abdominal wall and may lead to an abscess. This may be the first evidence of disease, so that caution is necessary in assuming that the hepatic lesion is secondary to an abscess of the abdominal wall. Rupture of an actinomycotic abscess near the surface of the liver into the general cavity of the peritoneum causes acute peritonitis, as in Grainger Stewart and Muir's case. But from the frequency with which perihepatic adhesions are found it is more usual to get localised collections of pus near the liver, such as a subphrenic abscess. An actinomycotic abscess may even perforate into the stomach.

In Duckworth and Marsh's² case an actinomycotic abscess in the left lobe of the liver eroded the stomach wall from without inwards; there was also a



FIG. 50.—Actinomyces of the liver, from a specimen (Series ix 182a) in St. George's Hospital Museum. (Drawn by Dr. E. A. Wilson.)

¹ Stewart, H. M. *Guy's Hosp. Rep.*, 1897, liv, 303.

² Duckworth and Marsh. *Brit. Med. Journ.*, 1900, ii, 1189; *Trans. Clin. Soc.*, 1901, xxxiv, 1.

subphrenic abscess of the same nature. In a man under my care an actinomycoma of the right lobe discharged into the stomach.

The abscess or abscesses in the liver may extend through the diaphragm into the lung or pleural cavity. Cases of hepatic actinomycosis may thus first present themselves as chronic empyemas of obscure origin. An actinomycotic tumour in the posterior part of the right lobe may spread into the right suprarenal, and even reach the right kidney.

The pus contains the characteristic granules composed of the ray fungus, and often pyogenetic cocci. It has been thought that suppuration is due to secondary infection, but there may be no evidence of mixed infection. Around the areas of suppuration there is fibrosis with pigmentation. Microscopically there are intercellular fibrosis and atrophy of the liver cells. The remainder of the liver may be fatty or lardaceous. In rare cases actinomycosis may be pyaemic and spread by the blood-vessels (DEAN).

In Kanthack's¹ case it was not clear whether the abscess originated in the right lobe of the liver or at the base of the right lung; from this it had spread by continuity into the right suprarenal, and had given rise to pyaemic abscesses over the body. In Boari's² case there were secondary pyaemic abscesses due to pyogenetic cocci and not containing actinomyces.

Actinomycotic lesions in the liver have sometimes been regarded as tuberculous or ordinary hepatic abscesses.³

A plate published in 1838 of "an organic disease of the liver of an obscure kind as yet undescribed," and shewing "breaking down of a peculiar tubercular matter," is clearly actinomycosis.⁴

Clinical Picture.—Before there are any symptoms or signs indicating disease of the liver there may be evidence of abdominal disturbance, such as pain, constipation, or localised swelling imitating appendicitis. Stewart laid stress on the occurrence of two stages in the disease—an early period just referred to, and a later one when the liver is definitely affected. Between these two stages there may be an interval of fair health. The first symptoms of hepatic actinomycosis may be those of an empyema, subphrenic abscess, of an abscess in the abdominal wall, or, when the portion of the liver near the kidney is involved, of a perinephritic abscess. The liver may be enlarged, and with fever and pain over the liver the resemblance to an ordinary hepatic abscess may be very close.

A girl, aged twenty-one, was admitted into St. George's Hospital in October 1904 with a history of three acute attacks of abdominal pain in the past twelve

¹ Kanthack. *Trans. Path. Soc.*, Lond., 1894, xlv, 233.

² Boari. *Atti Accad. d. sc. med. e nat. in Ferrara*, 1895-6, lxx, 247.

³ *Vide* Harley, *Med.-Chir. Trans.*, 1886, lxi, 135; Shattock, *Trans. Path. Soc.*, Lond., 1885, xxxvi, 260.

⁴ Anatomical Drawings from Collection in the Army Medical Museum at Chatham. 3rd Fascic., 1838. Printed by Taylor, London.

DEAN. Brit. med. Journ., 1912, ii, 1303

Second examination of the pus may be necessary before the organism is detected.

Opie has described a case of botryomycosis of the liver which might have resembled actinomycosis to the naked eye. This condition is due to an organism resembling the Staphylococcus pyogenes aureus

originally advocated by Thomassen
Iodide of potassium has long been regarded as the standard and specific remedy ~~for~~; But its value is very doubtful (Keynes); It should be given in large doses up to 300 grains daily. The fibrosis around the lesions may prevent the advent of the iodide, and the local injection of iodide or iodine is reasonable; Baracz reports good results from copper sulphate 1 per cent. solution, injected in a similar manner.

Opie. Arch. Int. Med., Chicago, 1913, XI, 425.
Thomassen. L'Echo Med., 1885
Keynes, G. St. Barth. Hosp. Rep., 1924, LVII, 71
Baracz, R. Zentralbl. f. Chir., 1922, XLIX, 634

months. The abdomen was opened and the appendix found to be normal, and a bilateral pyosalpinx removed but not examined. In January 1905 she was operated upon for a right subphrenic abscess, but she became very anaemic, and continued to have a hectic temperature until June 16, when she died with thrombosis of the right femoral vein and gangrene of the foot. At the necropsy there were subphrenic and hepatic abscesses shewing actinomyces, and the pyosalpinges which had been kept were then examined and found to be actinomycotic; the disease was therefore probably primary in the genital tract.¹

Jaundice is extremely rare. Ascites has been noted late in the disease (Eve²), but is usually absent. Anaemia is an important feature of the disease. There is leucocytosis. Latimer and Welch³ described a case of actinomycosis of the liver combined with myeloid leukaemia.

The **prognosis** of actinomycosis of the liver is very bad. Duvau⁴ collected 40 cases of hepatic actinomycosis, all of which proved fatal. Presumably the prognosis should be less gloomy if the disease could be recognised in an early stage and treated vigorously with iodide of potassium, and secondary infection with pyogenetic micro-organisms prevented. For when the latter event has occurred the prognosis is bad. Though much commoner in animals, actinomycosis is rather more virulent in man.

The **diagnosis** depends on finding the fungus in the pus either from the liver or from a discharging abscess elsewhere. Before this has been done the condition is hardly likely to be thought of, and recorded cases shew that the disease has been regarded as empyema, pulmonary tuberculosis, sarcoma of the kidney (Leith), perinephritic abscess, hepatic abscess, suppurative cholangitis due to gall-stones, suppurating hydatid, or gumma of the liver.⁵ It has been observed that the subjects of actinomycosis react to Koch's tuberculin (Kahler, Arloing); this might lead to an erroneous diagnosis of massive tuberculosis of the liver.

Treatment.—The effect of iodide of potassium on actinomycosis is extremely marked and does fully as much good as it does in tertiary syphilis. It should be given in large doses, as much as two drams, or even more daily. In addition, 15 to 30 minims of a 1 per cent aqueous solution of iodide of potassium may be injected into the affected part, at first at intervals of three or four days, but later more frequently (Sawyer⁵). The effects of iodides internally combined with x-rays have been very encouraging.

When an actinomycotic abscess has been opened, the necrotic tissue may be scraped away with advantage, while of course iodides should be given freely. Iodoform may be employed locally, and carbolic acid or other disinfectants should be applied in order to minimise the risks of

¹ Vide Symes-Thompson. *Brit. Med. Journ.*, 1907, i, 984.

² Eve. *Trans. Path. Soc.*, Lond., 1889, xl, 405.

³ Latimer and Welch. *Trans. Assoc. Am. Phys.*, 1896, xi, 328.

⁴ Duvau. *Thèse de Lyon*, 1902.

⁵ Sawyer. *Journ. Am. Med. Assoc.*, 1901, xxxvi, 1211.

infection. In a few cases tuberculin has seemed to have a good effect; Ziegler found the injection ~~of~~ a protein body obtained from cultures of *Staphylococcus pyogenes aureus* ~~of use~~, and a cure has followed the use of ~~the~~ autogenous vaccines (Wynn,¹ Harbitz and Grøndahl²). Arsenic ~~has~~ also been recommended (~~Brault~~).

have often
been used

LYMPHADENOMA

Synonyms: Hodgkin's Disease, Lymphomatosis granulomatosa.

In generalised lymphadenoma the liver may contain nodules of white growth. As a rule the growths are small, discrete, and do not lead to any enlargement of the organ during life, but there may be a large diffuse mass.

Congenital lymphadenoma has been described (Bouvain and Ducloux,³ Brault⁴), but the cases may have been pseudoleukaemia or lymphocytoma rather than lymphadenoma in the strict sense in which it is used ~~in this~~ ^{here} article.

Morbid Anatomy.—~~The appearances of~~ lymphadenomatous nodules in the liver may imitate caseous tuberculous masses and secondary new-growth. They are firm, white, and do not soften or become bile-stained; in these particulars they differ from what is often seen in advanced caseous tubercles. Tuberculosis may be combined with lymphadenoma in the liver (~~Andrewes~~), as is well shewn in a specimen (No. 2223^c) in St. Bartholomew's Hospital Museum. Lardaceous change may be found in a liver affected with lymphadenoma, and from the absence of any other factor, such as suppuration or syphilis, it would appear that lymphadenoma, or its underlying cause, may induce the lardaceous change.

Microscopical Appearances.—The growth starts in the portal spaces and extends outwards, ~~passing~~ between and eventually into the neighbouring lobules. The margin of the invaded lobules has an appearance like that of intercellular cirrhosis. Gradually the growth infiltrates the lobules, and the liver cells atrophy. The columns of deeply staining cubical cells, the so-called new bile-ducts, shew up prominently in the growth and at its advancing margin. In an early stage the growth is composed of small cells like lymphocytes, and the nodule closely resembles that of the earliest (miliary) collections of lymphocytes in lympho-

¹ Wynn. *Brit. Med. Journ.*, 1908, i, 554.

² Harbitz and Grøndahl. *Am. Journ. Med. Sc.*, Phila., 1911, cxlii, 386.

³ Bouvain et Ducloux. *Presse méd.*, Paris, 1901.

⁴ Brault. *Manuel d'histologie pathol.*, Paris, 1912, iv, part i, 1014.

⁵ Andrewes, F. W. *Trans. Path. Soc.*, Lond., 1902, liii, 313.

1) Colebrook, Keynes

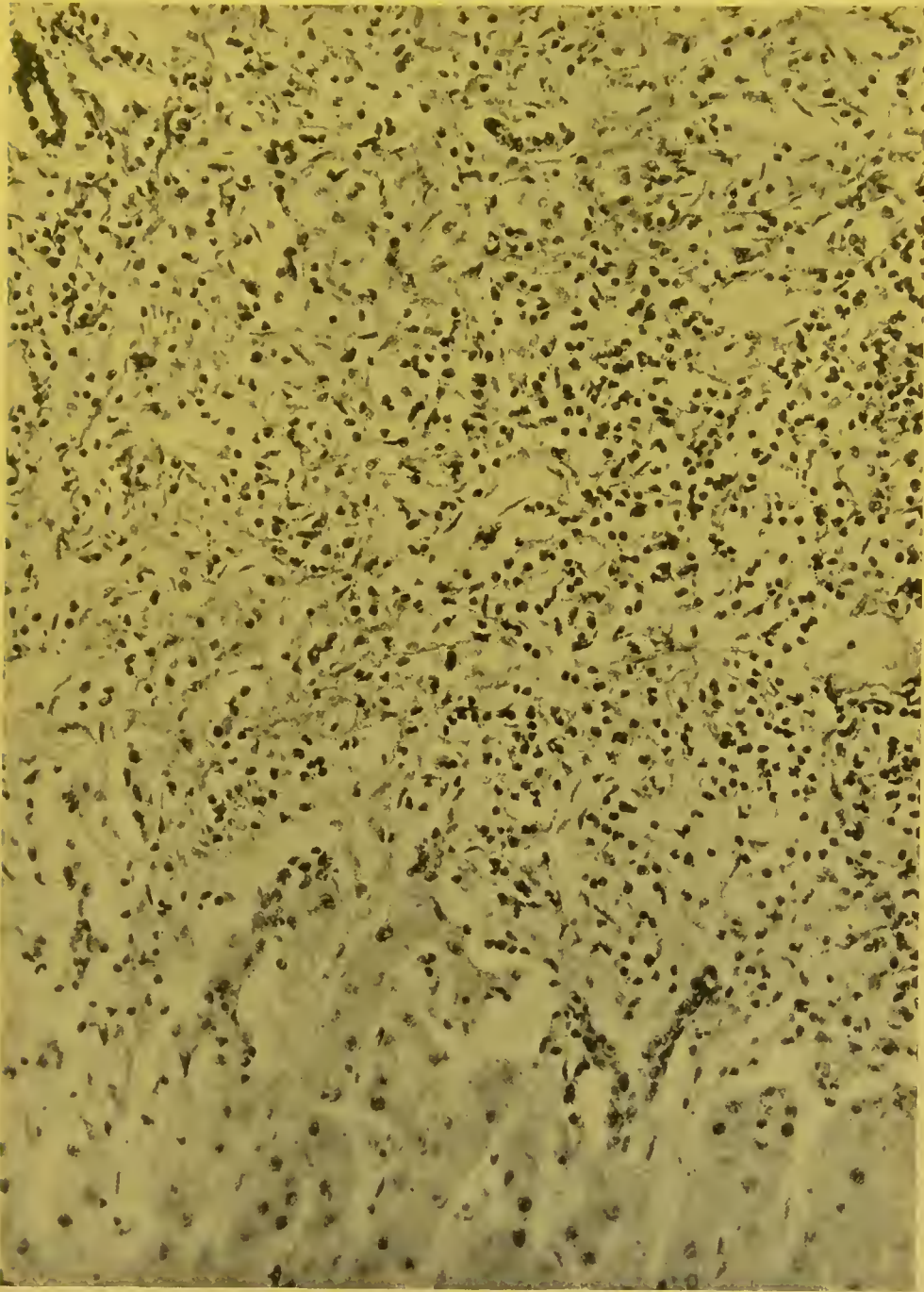
and SALVARSAN (Kellock) have

1) and see next

and, According to Symmers, ^{begins with} hyperplasia of lymphoid cells
in the wall of the portal vein; it passes

Colebrook, L. Lancet, 1921, i, 893

cytic leukaemia. Retiform tissue with cells like large lymphocytes and



Mr. New
has a
seller

FIG. 51.—Margin of lymphadenomatous nodule. The endothelial and connective-tissue cells forming the growth are well seen. There is a reticulum between the cells. In one part the formation of deeply staining pseudobile canaliculi from the liver cells can be seen. High power. (Dr. H. Spitta.)

multinuclear (lymphadenoma) cells then appear ; and in very chronic cases

2) , and for this and other reasons Oliver would class
Lymphadenoma with lympho-sarcoma and endothelioma.

~~Sternberg's~~

1) Symmers has reported a case in which the liver
was enormously and except for the spleen and abdominal
lymphatic glands exclusively affected.

Symmers, D Amer. Journ. Med. Sc., Phila., 1924, CLXVII,

Oliver. Journ. Med. Research, Boston, 1913, XXIX, 191

~~Sternberg~~

According to DÉVÉ multiplication of
hydrated cysts is due to stimulation or
injury; ~~also~~

HYDATID CYSTS

HYDATIDS (*ιδάρις*) are the cystic, larval, or bladder stage of a tapeworm which in its adult stage is found in the intestine of the dog, and also occurs in the wolf, the fox, and the jackal.

Life-History.—This tapeworm—the *Taenia echinococcus*—is small, measuring about 4 millimetres, or $\frac{1}{6}$ inch, in length, and composed of not more than four segments, the head and three proglottides, the last or terminal one being larger than the others put together, and containing fully developed sexual organs and, when fecundated, ova to the number of 500. The first segment, or head, has a prominent rostellum surrounded by two rows of hooklets, there being about 20 hooklets in each series. There are also four suckers. When the terminal proglottis breaks off from the tapeworm and is carried along with the faeces, the contained ova are liberated.

The ova after their exit from the bowel of the host are scattered about, and may find their way into the alimentary canal of man, when eaten on lettuce, water-cress, or other vegetables, or drunk with water. When the ova get into the stomach, their chitinous envelopes are dissolved, and an oval-shaped embryo, with six spines arising from one of its poles, is set free. The spines are directed backwards and thus allow the embryo to bore its way into the coats of the bowel, but prevent it from returning along the passage it has made. The embryos get into the portal vein and are conveyed to the liver. That they pass by the portal vein is largely assumed because the liver is *par excellence* their destination. If they simply bored their way straight through opposing structures, it would be natural to find them equally distributed throughout the surrounding organs. Possibly, moreover, conditions for their further development are more favourable in the liver than elsewhere, just as in the case of the free embryos of trichinella the muscles are the place of selection.

It has been thought that injury will favour the evolution of an embryo into a hydatid cyst by reducing the resistance of the liver. When the embryo reaches the liver and comes to rest, it proceeds to become transformed into the bladder or hydatid. The embryo loses its hooklets and enlarges so as eventually to form a small cyst; the outer surface becomes laminated and is called the ectocyst, while more internally the granular endocyst is evolved, and the contents undergo liquefaction. When reproductive changes leading to the production of daughter cysts commence, the first change is the formation of brood-capsules in the endocyst. These are small buds, lined internally by material resembling the ectocyst, and externally by the endocyst, so that it appears like an invagination of the cyst. The cavity of the brood-capsule contains fluid. From the outer surface of the brood-capsule the scolices develop; they are the early stage of the head of the future tapeworm and are provided with hooklets. The scolices arising from the outer surface of the brood-capsule eventually become invaginated into its interior. They readily become detached from the wall of the brood-capsule, and as a result of rupture of the brood-capsules become free in the cavity of the cyst. A scolex is about 0.3 mm. long and consists of two segments; the segment originally attached to the wall of the brood-capsule often contains crystals of carbonate of lime, while the

free segment has a crown of hooklets and four suckers. The hooklets measure 0.04 mm. Should the scolex reach the intestine of a dog it develops into an adult tapeworm by lengthening and transverse segmentation of its posterior end.

Daughter cysts are produced either inside the original cyst, endogenous formation, which is the usual way, or more rarely by external budding off, exogenous formation. The two processes may both occur in the same cyst. The daughter cysts are derived either from the scolices or brood-capsules, which become vesicular, or from invagination of the parenchymatous endocyst. The daughter cysts may become detached from the endocyst and become free in the cavity of the parent cyst, and may contain granddaughter cysts.

Exogenous formation of daughter cysts is rare in man, though common in sheep. Cysts are formed in the deeper layers of the ectocyst, become filled with fluid, and work their way outwards; they finally project from the surface of the mother cyst and become surrounded by an adventitious fibrous capsule. The mother cyst thus becomes knobby from the projection of daughter cysts, some of which may become disconnected from it. It is possible, however, that the so-called exogenous appearance is really only due to the cyst growing irregularly and sending out processes in the lines of least resistance. Pseudopodium-like processes of a single cyst might thus travel along the portal spaces in the liver, there being a continuous cavity throughout. Later the communication between the cyst and its process might become constricted, and in this way the appearance of a secondary cyst attached to the main cyst, but with an independent cavity, might be produced.

It was once thought that the extremely rare disease, alveolar hydatid, was a form of the exogenous proliferation of the hydatid cyst. In connexion with the exogenous mode of growth it may be pointed out that the presence of two or more hydatid cysts in the same liver is probably due to two distinct embryos having reached the liver and not to exogenous formation of one from the other.

Sterile Hydatid Cysts.—When no multiplication or reproductive changes take place in the cyst, it is spoken of as being sterile or as an acephalocyst, though the latter term is not often used now. The fluid does not contain any daughter cysts or scolices, and the nature of the cyst, whether hydatid or not, must be determined by microscopic examination of its wall. ~~Failure in reproduction~~ probably depends on ~~imperfect~~ nutrition. Pedunculated hydatid cysts which hang down from the under surface of the liver are more likely to be sterile than those embedded in the substance of the liver.

Warty ingrowths from the cyst wall are sometimes observed; they are probably abortive daughter cysts.

In the museum of Surgeons' Hall, Edinburgh, there is a part of the wall of a hydatid cyst shewing this papillomatous appearance. The cyst was a large one and contained many hundreds of small cysts (No. 1885).

On the other hand, it is possible that in some of the cases the warty growths were due to commencing degenerative changes and that the process is due to involution and not to imperfect evolution.

Structure of Hydatid Cysts.—The wall of the true parasitic cyst consists of the outer cuticle, or ectocyst, and an inner lining, or endo-

In children 90 per cent of the cysts are
single and without daughter cysts (DÉVE).

cyst. The cysts have an opalescent whitish-blue colour, and unless considerably thickened, tear easily. The ectocyst is elastic and tends to curl up when it is incised. Structurally it has a characteristic laminated appearance. There are wavy bands of homogeneous, hyaline material which, like the wall of the original ovum, is chitinous.

The endocyst forms the parenchymatous or granular internal lining of the ectocyst; from it the brood capsules are developed. It may contain crystals of carbonate of calcium like those seen in the mature cestoda and in the scolices. According to Loeper¹ the presence of glycogen shews that the cyst is living. The fluid in a living hydatid cyst is clear, of a low specific gravity, 1002 to 1015, contains no albumin, but a considerable quantity of chloride of sodium; for other details see page 405. When the cyst becomes inflamed or dies, the fluid becomes albuminous and may be turbid.

Outside the parasitic cyst, as a result of compression and irritation of the tissues of the liver, a fibrous capsule is produced which extends for a short distance into the surrounding liver substance. A hydatid cyst projecting from the surface of the liver may have a thick fibrous covering with the consistence of cartilage, which resembles a corneal fibroma of the spleen and may be calcified. The remains of the hydatid cyst may escape notice, and the true nature of these thick-walled cysts be overlooked. When embedded in the substance of the liver the fibrous capsule contains pseudobile canaliculi and mononuclear and eosinophil cells (Loeper, Bodin and Fiessinger²). This local eosinophilia is not constant, and corresponds in this respect more or less with the presence or absence of haemic eosinophilia (Dévé³). In addition, there may be giant cells whose function is to attempt absorption of the cyst; they do not contain tubercle bacilli, and differ from the giant cells of tuberculous granulation-tissue in that their nuclei are in the centre and not at the periphery. In rare instances the mother cyst may disappear; Stirling⁴ reports a case with more than 28,000 daughter cysts in which barely a shred of the mother cyst could be detected.

Two cysts arising in close contact to each other may be enclosed in the same pseudocyst or capsule derived from the tissues of the liver by pressure irritation. Occasionally a hydatid cyst is divided into two parts by a constriction, and thus resembles an hour-glass or a shirt stud. This may depend either on two cysts, originally separate, opening into each other, or, as pointed out in speaking of exogenous formation of daughter cysts, on irregular growth due to differences in the resistance offered by the surrounding tissues or by extrahepatic adhesions.

Situation of Hydatid Cysts in the Liver.—The cysts may be deeply embedded in the liver, and are naturally, from the greater size of the right lobe, commoner there than in the left lobe. Cysts in the upper and

¹ Loeper. *Clinique médicale de l'Hôtel-Dieu*, 1906, v, 264.

² Bodin et Fiessinger. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1908, xxv, 182.

³ Dévé. *Compt. rend. Soc. Biol.*, Paris, 1905, lvii, 49.

⁴ Stirling. *System of Medicine* (Allbutt and Rolleston), 1907, ii, part ii, 1004.

back part of the right lobe push the diaphragm up. Not uncommonly a hydatid cyst hangs down from the liver like a dilated gall-bladder.

Number.—There may be one cyst only, but it is not by any means rare to find two or three. ~~As many as forty small cysts have been found in the liver (Dolbeau).~~

Size.—A single hydatid cyst may reach a very large size indeed. The largest hydatid cyst of the liver on record appears to be one containing 36 pints; it occupied three-quarters of the abdomen and was successfully operated upon by H. B. Robinson;² four years previously it had been tapped and 40 litres (70 pints) removed with only very temporary relief.

Spontaneous Death.—Inasmuch as hydatids are most commonly present in the liver, being found there in ~~5~~ ¹/₇₅ per cent of all the cases of the disease, it is natural that hydatid cysts which have become latent, and undergone involution changes ending in spontaneous cure, are commoner in the liver than elsewhere.

(DÉVÉ) | ¹ It has also been thought that they are more often found in the liver because their natural evacuation is less easy than in the case of the lung or kidney, from which they may be coughed up or passed into the ureter. But there is not much difference between the lumen of the common bile-duct and of the ureter, except that the larger end of the ureter, the pelvis of the kidney, is directed towards the hydatid in the kidney, whereas the intrahepatic bile-ducts are small. This explanation of the frequency of hepatic hydatids is not worth much, for natural evacuation is rare in any organ and much less common in the lung and kidney than in the liver.

Causes of Spontaneous Death.—Possibly the cause may sometimes be inherent in the individual parasite, which, being of poor vitality, runs its allotted course and dies before reaching the ordinary size. For death with spontaneous cure is most often seen in small cysts which have not given rise to symptoms during life. This, however, is not a universal rule, and a large hydatid, if not operated on, may gradually undergo involution changes and shrivel up.

A patient had been seen when eleven years old by Sir Astley Cooper, and his liver was then said to be four times its natural size and was thought to contain fluid; no operation was done. The tumour gradually got smaller and forty-five years later, when Murchison³ saw the patient, there was a mass as hard as bone in connexion with the right lobe of the liver.

The usual term of life of a hydatid cyst is not known, but it has been thought to be as long as twenty years. Of the causes acting from without and impeding the growth or possibly poisoning the parasite outright, the most commonly recognised is the entrance of bile into the cyst. The constant pressure exerted by the contents of the tense cyst leads to atrophy of the tissues intervening between the cavity of the cyst and an adjacent bile-duct and allows of the entry of bile into the cyst, and sometimes of a discharge of the contents of the cyst into the bile-duct (*vide*

¹ Dolbeau. *Bull. Soc. Anat.*, Paris, 1857, xxxii, 116.

² Robinson, H. B. *Trans. Clin. Soc.*, Lond., 1897, xxx, 16.

³ Murchison. *Lectures on Diseases of the Liver*, p. 130, 1877.

Chauffard argues that cysts may develop primarily in the gall bladder, the embryo entering the gall bladder from the cystic veins which open into the portal vein.

1 D'ÉVÉ refers to cases in which
60 and 51 cysts were found in
the liver

Chauffard. Ann. de méd., Par., 1910, V, 561.

D'ÉVÉ. Compt. rend. Soc. Biol., Par., 1913, LXXIV, 781.

D'ÉVÉ Compt. rend. Soc. Biol., Par., 1913, LXXIV, 735

p. 418.) As evidence of the entrance of bile into the cyst the occurrence of crystals of bilirubin and biliverdin may be forthcoming.

On the other hand, dead cysts may not contain any trace of bile, and spontaneous cure of hydatid cysts may occur in other organs, where, of course, bile can play no part. Further, the parasitocidal action of bile appears to be slight, as Dévé¹ finds that scolices continue to grow in a mixture of equal quantities of bile and hydatid fluid. Secondary hydatid cysts can develop in the peritoneum when there is a bile-stained peritoneal effusion from rupture of a hydatid cyst, already communicating with a bile-duct, into the peritoneal cavity. It therefore seems probable that bile has little to do with spontaneous death of hydatid cysts in the liver. In some instances the entrance of bile is subsequent to the death of the parasite.

Chemical alterations in the lymph bathing the outside of the cyst have also been suggested, and it has been thought that poisonous products absorbed from the bowel, such as alcohol, might play such a part; but the resistance of hydatid cysts to any form of drug renders this doubtful. The entrance of fluids, such as blood, into the cavity of the cyst may so disturb the equilibrium necessary for the continued life of the parasite as to lead to its death. Of the occurrence of past hæmorrhage into a hydatid cyst there is no very satisfactory evidence, as the crystals of hæmatoidin and bilirubin are identical. It appears probable that in cases in which "hæmatoidin" is described in cysts the crystals are really bilirubin.² Absorption of the contained hydatid fluid has been thought to be the cause of spontaneous death of the parasite; this view is supported by cure after simple tapping of a cyst, but, on the other hand, there is no proof that under ordinary conditions absorption of the fluid can occur from a living cyst.

The rapid proliferation of the daughter cysts so that they increase out of all proportion to the surrounding fluid and produce heightened pressure, and so exert an inhibitory influence on the life of the parasite, has been put forward as a cause of spontaneous death.³ That this is not a universal cause is shewn by the fact that dead cysts may contain few or even no daughter cysts. Changes in connexion with the fibrous capsule of the cyst, such as cicatricial contraction and calcification, have also been thought to interfere with the nutrition of the parasite, but it is difficult to prove the relation between the two processes.

Changes following Death of a Hydatid Cyst.—The fluid of a living hydatid cyst under ordinary conditions is practically free from albumin; after death, however, it becomes albuminous. From the albuminous fluid removed from a hydatid cyst which had previously been killed by electrolysis Boinet⁴ obtained crystals of a toxic body analogous to mytilotoxin, probably the result of cleavage of the albumin. The albuminous fluid in

¹ Dévé. *Compt. rend. Soc. Biol.*, Paris, 1903, iv, 75.

² Vide Dickinson, W. L. *Trans. Path. Soc.*, Lond., 1894, xlv, 259.

³ Murchison. *On Diseases of the Liver*, p. 62, 1885.

⁴ Boinet. *Rev. de méd.*, Paris, 1898, xviii, 845.

the cyst becomes turbid and cloudy from the precipitation; later, absorption occurs and the contents become less fluid and more gelatinous and the parent cyst shrinks, while fatty metamorphosis of the albumin gives the contents a buttery, caseous, or putty-like character; various stages, from a glairy or colloid state to complete solidity, may be met with as time goes on. The contents are frequently yellow in colour. These

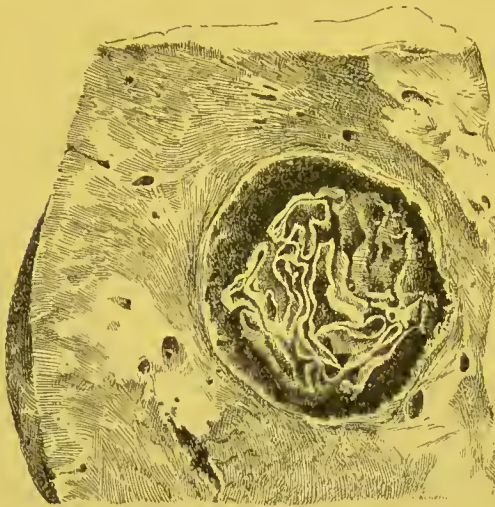


FIG. 52.—An obsolete hydatid cyst in the liver. From a specimen (Series ix. No. 179e) in the Museum of St. George's Hospital. (Drawn by Dr. E. A. Wilson.)

changes in the mother cyst are subsequently repeated in the daughter cysts. The putty or gelatiniform material may contain crystals of cholesterin, stearin, bile pigment, tyrosine, Charcot's crystals;¹ and calcification may extend from the outer adventitious capsule into the contents of the cyst.

Contraction and shrinking of the outer fibrous capsule lead to a folding of the cyst wall compared to the appearance of a corpus luteum. The outer capsule may become extremely hard from infiltration with carbonate and phosphate of lime. Good specimens of the calcified shells, so to speak, of hydatid cysts are

to be found in most museums; there is one (No. 2234) in St. Bartholomew's Hospital Museum of multiple calcified cysts. Usually the process of spontaneous cure is unaccompanied by any inconvenience or clinical signs.

In a case recorded by Mitchell Bruce and Sheild² the contents of a very large cyst became gelatiniform. The tumour was so large, and was, contrary to what would naturally be expected, increasing in size, that laparotomy was performed. The diagnosis of a solid hydatid cyst had previously been made by aspiration of colloid matter containing hooklets.

In rare cases a spontaneously cured hydatid suppurates and, if in communication with the bile-ducts, may cause suppurative cholangitis.

Condition of the Remainder of the Liver.—The pressure exerted by a large cyst causes atrophy of the liver in its immediate neighbourhood, and in this way a whole lobe may become excavated and destroyed. In extreme instances the organ may become so deformed that its anatomical features are quite obliterated. Compensatory hypertrophy of other parts of the liver readily occurs, and the resulting hypertrophy is often considerably in excess of the normal amount of liver substance. The left

¹ Carwardine. *Trans. Path. Soc.*, 1898, xlix, 132.

² Mitchell Bruce and Sheild. *Med.-Chir. Trans.*, Lond., 1892, lxxv, 175.

For cases of malignant disease and ^{hydatid} cysts
vide Winkler's J.H.K. Rep 10, 16, 17, 42.
Lent 5, 2.

lobe has been found to weigh as much as a normal liver (Zadoc-Kahn¹). The compensatory hyperplasia occurs with greater ease in hydatid disease of the liver than in cirrhosis, malignant disease, or abscess. This is probably because there is no depressing factor, such as toxins, to reduce the vitality of the liver cells. The compensatory hypertrophy is better developed at some distance from the cysts, and since cysts are usually in the right lobe, the left is frequently greatly hypertrophied, though the quadrate and Spigelian lobes share in the compensatory process. This compensation accounts for the absence of constitutional symptoms in the disease. On the other hand it is possible that the hyperplasia of the liver cells may be so excessive as to give rise to primary carcinoma, as in Loehlein's case. With very rapidly growing hydatid cysts there may not be time for compensatory hypertrophy to occur, and the amount of liver substance may for a time be greatly diminished. Hydatid cysts have been found to be associated with universal cirrhosis of the liver² (Cayley, Weir, S. Savage³), and with malignant disease.³ In Necker's⁴ case there were two hydatid cysts, cirrhosis, secondary spindle-celled sarcoma, and a primary carcinoma derived from the bile-ducts. In a man aged forty-nine who died in St. George's Hospital from pyloric carcinoma with extensive secondary infection of the liver, which weighed 10 pounds, there was a dried-up hydatid cyst in the right lobe close to the gall-bladder. In a case recorded in St. Thomas's Hospital Reports primary carcinoma of the liver was associated with several calcified hydatid cysts.⁵ In Loehlein's case of a very large hydatid of the liver there was hyperplasia of the liver cells and a primary carcinoma derived from the liver cells. Loehlein⁶ quotes 4 other cases by Bamberg, Dibbelt, Necker, and Fränkel.

In a case recorded by Pitt⁷ the irritation set up by a cyst in the left lobe of the liver of a man aged thirty-nine years, who had contracted syphilis thirteen years before death, seemed to have caused a remarkable syphilitic growth enclosing the cyst.

Relative Frequency of Hepatic to Hydatid Cysts Elsewhere.—The liver is more often the site of hydatid cysts than the whole of the remainder of the body. The percentage incidence of hydatids in the liver is variously estimated ~~at 74 per cent (Lyon⁸)~~ to 44 per cent (Davaine⁹).

a / 5000 77
per cent.
(DÉVÉ)

¹ Zadoc-Kahn. *Arch. gén. de méd.*, Paris, 1897, clxxix, 171.

² Cayley, W., *Trans. Path. Soc.*, Lond., 1874, xxv, 129; Savage, S., *Brit. Med. Journ.*, 1899, i, 1030; Weir, *Med. Rec.*, N.Y., 1899, lv, 149; Stevens, *Brit. Med. Journ.*, 1901, i, 1139. TABOADA. *Cronica Med.*, Lima, 1921, 39, 296.

³ Habran, *Bull. Soc. Anat.*, Paris, 1868, p. 437; Florand, *ibid.*, 1886, 4. s., xi, 677; Longuet, *Gaz. hebdom. de méd.*, Paris, 1874, xxi, 774; Russell, J. W., *Brit. Med. Journ.*, 1907, i, 311; Cranwell, *Bull. et mém. Soc. de chir. de Paris*, 1909, xxxv, 3. *Moderna. Patologica*, 1921, 833.

⁴ Necker. *Ztschr. f. Heilk.*, Wien u. Leipzig, 1905, xxvi (Abt. path. Anat.), 351.

⁵ St. Thomas's Hosp. Rep., 1891, xxix, 141.

⁶ Loehlein. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1907, xlii, 531.

⁷ Pitt, G. N. *Trans. Path. Soc.*, Lond., 1886, xxxvii, 276.

⁸ Lyon. *Ann. Journ. Méd. Sc.*, 1902, cxxiii, 124. DÉVÉ, F. *Arch. de méd. de enf.*, Par., 1918, xxi, 225.

⁹ Davaine. *Traité des Entozoaires*, Paris, 1878.

In 1897 cases of hydatid disease Davies Thomas¹ found the liver affected in 1084, or 57 per cent, the lungs being next with 220, or 11.6 per cent. Finsen estimated the incidence of hydatids in the liver at 69 per cent, Peiper² at 66.4 per cent, Neisser³ at 50 per cent, and Cobbold, on the basis of his own and Davaine's cases, at 46 per cent.

The frequency with which the liver is infected is due to its filtering the blood from the intestines and thus arresting the embryos which have got into the portal vein. If the embryo is not stopped by the liver, it passes to the capillaries of the lung and may come to rest there.

Etiology.—*Geographical Distribution.*—In England hydatid disease is said to be commoner in London than in most country districts, but in the Fen districts around Cambridge it is comparatively common.

Murchison in 2100 necropsies at the Middlesex Hospital recorded 13 bodies with hydatids, or 1 in 161; in 7 of these, or 1 in 300, they were the cause of death. From an examination of the statistics of in-patients at St. Bartholomew's Hospital, London, for thirty years, W. S. Church⁴ found that one case of hydatid disease was admitted in 1100. The disease appears to be getting rarer in London.

In Scotland hydatids are very rare, but in Shetland they are comparatively common (H. Stiles⁵). In Russia they are not infrequent. In Switzerland and South Germany, where the alveolar form occurs, the cystic form is not common. ~~In Iceland they are extremely common; estimates vary from one sixth to one fifty eighth of the entire population, one thirtieth being the mean and more probable figure.~~ The great frequency of hydatid disease depends on the enormous number of dogs which are very frequently infected with taeniae. It is said to be common in Turkey. Hydatid cysts are rare in South Africa, but are becoming more frequent in Algiers, and are not uncommon in Egypt. In Australia they are very frequent, being commonest in South Australia. In 1000 necropsies mentioned by Stirling and Verco hydatids were found in 49, or 5 per cent. In Victoria one case of hydatid occurs in every 175 admitted to hospital, in New South Wales 1 in 380. The proportion in New Zealand and Tasmania is also very high (Church). Stirling and Verco⁶ lay stress on the presence of large numbers of sheep as an important factor in the incidence of hydatid disease. In North Queensland it is almost unknown.

In North America hydatid disease is rare, and when it is met with is in the bodies of foreigners.

Up to July 1891, Osler⁷ could only find evidence of 85 cases; since the migration of Icelanders into Winnipeg the disease has become more frequent in

¹ Thomas, Davies. *Hydatid Disease*, Adelaide, 1894.

² Peiper. *Thierische Parasiten*, 1904, S. 158.

³ Neisser. *Echinococcenkrankheiten*, Berlin, 1877.

⁴ Church, W. S. *Clin. Journ.*, Lond., 1900, xv, 337.

⁵ Stiles, H. *Scot. Med. and Surg. Journ.*, 1903, xii, 131.

⁶ Stirling and Verco. *System of Medicine* (Allbutt and Rolleston), 1907, ii, part ii, 997.

⁷ Osler, W. *Practice of Medicine*, ed. ii.

and Tunis/1

^ Out of 2,727 cases DEVE found the liver primarily affected in 75 per cent, the lungs being next with 8.5 per cent.

^ In France hydatids are not frequent, but are less rare in the Landes and in Rouen. In Iceland there were extremely common; fifty years ago 1 in 40 of the inhabitants were affected, now the estimate is 1 in 2000 (Sambon).
In 1917 hydatid disease was responsible for 14 per cent. of the mortality.

DEVÉ. Compt rend. Soc. biol., Paris, 1913, LXXIV, 735

Sambon, L.W. Journ. Trop. Med. and Hyg., London, 1925, XXVIII, 47.

that locality. Ten years later Lyon¹ collected notes of 241 cases of hydatid disease occurring in the United States and Canada up to July 1, 1901. Most of the patients were either Icelanders or Germans.

In the Argentine Republic hydatid disease has been becoming increasingly common; in the years 1890–1907 there was 3195 cases treated in the hospitals of Buenos Aires (Cranwell²). This depends on the large number of sheep and dogs there. Hydatid disease is very rare in India, and doubt has been expressed as to its origin there at all; it may be found in persons dying in India who have acquired the disease elsewhere. W. J. Buchanan³ records an undoubted case of hydatid cyst of the liver in a native of India who had never been out of the country; a very large abdominal hydatid cyst, possibly hepatic in origin, was recorded by Sorabji⁴ in a native Indian woman. It is very rare in China.

There is nothing to suggest that the natives of Iceland or Australia, where the disease is most prevalent, are in the slightest degree immune from hydatid disease. In 1897 Verco and Stirling⁵ stated that except for accident and tuberculosis, hydatid disease was responsible for all deaths of the aborigines in the Adelaide Hospital.

Method of Infection.—The ova derived from the dried and scattered faeces of dogs may settle on vegetables or contaminate drinking-water. Lettuce and especially water-cress may, if not carefully washed, serve as vehicles for the transmission of the disease. Persons in contact with dogs and other animals, the subjects of *Taenia echinococcus*, are in danger of becoming the hosts of the bladder stage of the tapeworm. There is some risk in the possession of pet dogs, as infection may be conveyed by a dog licking the hands and face of its master. Duvé⁶ collected a number of instances of two cases of hydatid disease occurring in the same family.

It has been suggested that when portions of hydatid cysts embedded in the livers of sheep or oxen are eaten, the scolices may develop in the alimentary canal of man and give rise to auto-infection. This hypothesis requires for its confirmation the recognition of scolices in the human alimentary canal, and has not yet been justified. Offal from slaughter-houses, however, containing hydatid cysts is a most important factor in the causation of the tapeworm in dogs, and so indirectly of the cysts in man.

Sex.—The incidence of hydatid disease in the two sexes depends on their relative exposure to infection, which is generally more marked for men. In Australia, where the water-supply in the bush is the great source of infection, the ratio is 100 men to 77 women. In America Lyon found the incidence 60 per cent in men and 40 per cent in women.

¹ Lyon. *Am. Journ. Med. Sc.*, 1902, cxxiii, 124.

² Cranwell. *Bull. et mém. Soc. chir. de Paris*, 1909, xxxv, 3.

³ Buchanan. *Lancet*, 1900, ii, 19.

⁴ Sorabji. *Lancet*, Lond., 1908, i, 97.

⁵ Verco and Stirling. *Allbutt's System*, 1897, ii, 1114.

⁶ Duvé. *Arch. gén. de méd.*, Paris, 1907, cxviii, 673.

In France Davaine¹ found the incidence equal in the two sexes. In Berlin women were more often affected than men in the ratio of 65 to 35 (Neisser²), and in Iceland women are twice as often affected (71 per cent) as men (29 per cent) (Finsen³). \wedge

Cysts appear to grow more rapidly in children
~~Age.—The disease becomes more frequent up to about fifty years of age and then declines, the majority of cases occurring between twenty and forty. It is rare under fifteen. In children it is said to be less rare in girls than in boys, and to attract attention chiefly about eight years of age.~~

~~Pontou⁴ collected 22 cases in children in 1867, and a large number have since been recorded. In Australia during seven years Downs⁵ operated upon 25 cases. Cases of two cysts in the liver of a boy aged six years (H. B. Robinson⁶) and a boy aged seven years (Cheney⁷) have been recorded. Of 948 cases in the Argentine 135 occurred in the first, and 200 in the second decade of life (Vegas and Cranwell).~~

CLINICAL PICTURE.—Symptoms.—A hydatid cyst of the liver may remain entirely latent, so that its presence, even when involution or spontaneous cure have not supervened, may be only revealed at the necropsy, or be suspected for the first time when the abdomen is examined, in the course of life insurance routine or in a pregnant or recently delivered woman. Even when the cyst is large, there may be nothing to attract the patient's attention, except perhaps the increasing size of the abdomen, or a feeling of weight or of dragging in the hepatic region. \wedge When the capsule of the liver is inflamed, tenderness and pain on respiration are present, but acute perihepatitis is infrequent in the absence of suppuration. Pain in the right hypochondrium shooting to the right shoulder may be due to adhesions caused by the toxic action of hydatid fluid (Quénu⁸). ~~Maclaurin⁹ found that pain occurred in 62 out of 102 cases. Pain is quite rare in children.~~ The contrast between the marked physical signs and the freedom from symptoms and from constitutional disturbance has already been referred to. Pressure symptoms are, as a rule, absent; this probably depends on the slow growth of the cyst. Pressure on the stomach and intestines may, however, give rise to dyspepsia, vomiting, and constipation. Obstruction is a most exceptional result of hydatid cysts, but Reichold¹⁰ recorded the case of a woman in whom intussusception had been diagnosed. Upward pressure on the diaphragm may greatly encroach on the pleural cavity and produce considerable dyspnoea. This will be more marked when the abdomen is

¹ Davaine. *Traité de Entozoaires*, Paris, 1877.

² Neisser. *Die Echinococcenkrankheiten*, 1877.

³ Finsen. Quoted by Lyon.

⁴ Pontou. *Thèse de Paris*, 1867. Quoted in *Traité des maladies de l'enfance*, iii, 195.

⁵ Downs. *Austral. Med. Journ.*, 1911, xvi, 127.

⁶ Robinson, H. B. *Lancet*, Lond., 1899, i, 767.

⁷ Cheney. *Arch. Pediat.*, 1897, xiv, 851.

⁸ Quénu. *Rev. de chir.*, Paris, 1910, xlii, 945.

⁹ Maclaurin. *Austral. Med. Gaz.*, 1909, xxviii, 295.

¹⁰ Reichold. *München. med. Wchnschr.*, 1897, xlv, 441

1) Out of 644 in the Argentine 328 were females & 316 males (Vegas and Gramswell).
sex does not appear to exert any influence (Vegas and Gramswell, D. Prat), and in South America about 25 per cent of the cases occur in childhood.
Vegas and Gramswell collected 419 ^{children from} cases in the Argentine.

1) and 262 in the third

1) Pain as a rule is absent, ^{especially in children;} but it may be due to various complications. Out of 102 cases MacLaurin found a history of pain in 62.

1) { Omental adhesions or epiploitis ~~may also cause pain~~, and the pressure of a cyst, deeply embedded at the back of the liver, on the nerves of the ~~ab~~ body wall may cause pain. Pain resembling that of biliary colic may be due to pressure on the ducts or to the presence of cysts inside the ducts. According to Chauffard pseudo-biliary colic is more often due to pressure on the ducts than to intrabiliary hydatids, and biliary colic may be due to spasm caused by the irritation of toxic hydatid fluid.

Prat, D. Rev. med. del Uruguay, 1913, 467

Chauffard. Ann. de Méd., Paris, 1917, 4, 561

In one exceptional case asthma
has been ascribed to the
presence of a hydatid cyst (Rénou
and Jacquelin) | ^

Rénou et Jacquelin. Bull. Acad. de Méd., Paris, 1921. 3^e s^{érie}.
LXXVI, 204

distended from some other cause, such as pregnancy. The irritation of a large hydatid cyst may set up slight pleurisy and give rise to pain and cough. As in some other hepatic conditions, the pain may be referred to the right shoulder.▲ Epistaxis, haematemesis, melaena, and metrorrhagia have been recorded, but are extremely rare.

In a case recorded by Hillier¹ haemorrhage took place into a hydatid cyst and ran along the hepatic duct, which opened into the cyst, to the duodenum. The patient died from haematemesis and melaena. At the necropsy the cyst contained 37 ounces of blood-clot.

The physical signs of hydatid cysts are more prominent than the symptoms. In many instances the upper segment of the abdomen on the right side and in the epigastrium is prominent and firm, and there is bulging of the costal arch on the right side. In great abdominal distension lineae albicantes may be present. Dilated subcutaneous veins are very exceptional, but a prominent "caput Medusae" has been noted when the inferior vena cava is compressed by a large cyst.

The liver is enlarged, its form and outline varying, of course, with the position of the cyst or cysts. A cyst near the convexity of the liver displaces the diaphragm upwards. A cyst in the right lobe may compress the lower lobe of the right lung and imitate a pleural effusion. In rare instances a cyst in the left lobe has simulated a pericardial effusion.

When the cyst is deeply embedded in the substance of the right lobe, the liver is expanded and pushed forwards as if occupied by a solid growth. When the cyst projects from the under surface of the right lobe, the liver is pushed forward, and when it protrudes beyond the lower border it may imitate an enlarged and distended gall-bladder, a tumour of kidney, uterus, or ovary, or a pancreatic cyst. A pendulous hydatid cyst may, like a distended gall-bladder, be accompanied by a linguiform lobe of the liver. A cyst growing from the anterior surface bulges the hypochondrium out, or when in the left lobe, the epigastrium forwards, in a remarkable manner. In such cases the enlargement of the liver is not uniform, as in cirrhosis, but is localised and may be manifestly due to a tumour, in size varying from that of an orange upwards. The hepatic enlargement does not depend entirely on the position of the cyst, though of course it is chiefly due to its presence. When the right lobe is occupied by a large hydatid cyst, marked compensatory hypertrophy of the left lobe may render it easily palpable. Chauffard recorded such a case in which the left lobe weighed almost as much as a normal liver.²

Usually the tumour is tense and elastic; it may, especially when thick-walled and covered by liver tissue, give the impression of a solid tumour; as already mentioned, the contents may in exceptional cases undergo gelatinous change, although the cyst is increasing in size. Occasionally, on the other hand, it may fluctuate so as to imitate an abscess. On percussion the cyst is almost always dull; the entrance of air from

¹ Hillier. *Trans. Path. Soc.*, Lond., 1856, vii, 22.

² Chauffard. *Semaine méd.*, Paris, 1896, xvi, 265.

rupture into a hollow viscus, bronchi, or intestine being so rare as to make it probable that when the cyst appears to be resonant it is really covered by stomach or intestine. Gas has, however, been found in suppurating hydatid cysts without there being any communication with the intestinal tract, and can be explained as the result of infection with the *Bacillus aerogenes capsulatus* or other, usually anaerobic, organisms.

Dévè¹ collected 48 cases of gaseous hydatid cysts of the liver; 24 of these were closed suppurating cysts, 11 had ruptured into the bronchi, 7 into the alimentary canal, and 6 had been operated upon.

The "hydatid thrill," discovered by Blatin in 1801, is an inconstant sign and, even when present, is not pathognomonic. It is brought out by percussing the middle finger of the left hand when placed over the cyst; a peculiar vibration is then communicated to the finger percussed. This thrill was thought by Briançon² to be due to the impact of contained daughter cysts, but it can be obtained in sterile hydatid cysts, in tense cysts of other kinds, such as hydronephrosis, and sometimes in encysted ascites, or, according to Chauffard,³ in general ascites under certain conditions, such as an elastic state of the abdominal walls in young persons. The "hydatid thrill" is not very often obtained, but the conditions required for its production are more often realised in hydatid than in other cysts; so that its presence, though not absolute evidence, strongly suggests a hydatid cyst. Lancereaux⁴ obtained it twice in a personal experience of 60 cases; many observers have never met with it. A thrill is said to be relatively less rare in early life than in adult patients (Broca⁵). It has been thought that the occurrence of suppuration, by altering the conditions inside a hydatid cyst, will remove the thrill (Milian⁶). After tapping a cyst a thrill sometimes becomes evident, though previously absent.

When two or more hydatid cysts are either in or in connexion with the liver, the signs may be very confusing, and from the irregularity of the surface suggest malignant disease, cirrhosis with great enlargement, displacement of the liver, or affections of other organs.

In a case of multiple hydatids in the liver encroaching above on the pleural cavity, the downward projection of two large cysts from the right lobe of the liver left a notch between them which during life was taken for the notch between the two lobes of the liver, the organ being thought to be displaced downwards by a pleural effusion. Two hydatid cysts in a boy aged seven projecting from the anterior surface of the right lobe gave rise to a sulcus which when felt through the abdominal walls imitated the colon passing over a tumour of the right kidney (Cheney⁷).

¹ Dévè. *Rev. de chir.*, Paris, 1907, xxxv, 529.

² Briançon. *Thèse de Paris*, 1828.

³ Chauffard. *Traité de Médecine* (Bouchard et Brissaud), 1902, v, 303.

⁴ Lancereaux. *Traité des maladies du foie et du pancréas*, p. 738, 1899.

⁵ Broca. *Semaine méd.*, 1901, xxi, 89.

⁶ Milian. *Bull. Soc. Anat.*, Paris, 1900, lxxv, 911.

⁷ Cheney. *Arch. Pediat.*, 1897, xiv, 851.

1) Skeagraphy.
A calcified hydatid cyst has been shown to give an opaque shadow (Chauffard)

Chauffard. Bull. Acad. de méd., Paris, 1920, 3^e sér., Lxxxiv, 160

I have seen displacement
of the heart to the right
of the sternum by a
Cyst connected with the
left lobe of the liver.

Cignozzi, O. Lyon méd., 1925, xxii,

Pressure on the bile-duct producing jaundice, on the portal vein inducing ascites or hæmorrhoids, or on the inferior vena cava causing oedema of the legs, is ~~very~~ rare. The position of the cyst has an important bearing on the production of these pressure symptoms; thus, a cyst in the portal fissure or in the Spigelian lobe will readily give rise to these results (Tuffier¹). Pressure symptoms are relatively less infrequent in children than in adults. In 502 collected cases of hydatid cyst there were 44, or 8·7 per cent with jaundice (Quénu²). Jaundice is almost constant when a hydatid ruptures into and discharges daughter cysts into the ducts, but is rare apart from this, *though it may occur when the cyst is in the Spigelian lobe (Cignozzi)* ~~is more likely~~

Stirling³ describes a large cyst with calcareous walls springing from the under surface of the left lobe, which pressed on the common bile-duct and thus produced jaundice. A man with jaundice of eleven months' duration and well-marked xanthoma multiplex had three hydatid cysts in the liver; one of these projected into the portal fissure and completely obliterated the common hepatic duct (W. Legg⁴). It has been thought that osmosis of hydatid fluid into the tissues around the cyst may cause cholangitis and jaundice (Quénu).

A large cyst may in rare cases compress the inferior vena cava and produce oedema of the lower limbs and the trunk, and a plexus of dilated veins over the abdomen (Pheasants⁵), but complete obliteration of the inferior vena cava without oedema of the feet has been recorded (Dévé⁶). A pendulous cyst is rather more likely to press on the inferior vena cava or right iliac veins than a cyst embedded in the liver. Ascites is practically always due to some complication; thus it occurs when there is leakage of the cyst after aspiration or spontaneous rupture. When suppuration has supervened in the cyst, ascites may be due to concomitant local peritonitis. Large cysts naturally displace neighbouring viscera, the amount of displacement depending on the size and situation of the cyst. The diaphragm is frequently pushed up on the right side, and when a large cyst occupies both lobes of the liver the two sides of the thorax may be greatly encroached upon. In such cases or when the cyst is in the left lobe the heart may be greatly displaced upwards. In Knaggs'⁷ case the cardiac dulness was in the first and second intercostal spaces. A large cyst may displace the stomach, the right kidney, and the other abdominal viscera. Occasionally urticaria is the first indication of a hydatid cyst, and may be seen in a case without any proof that the cyst has ruptured or leaked. In McMurray's⁸ case pruritus and a papular rash existed for two years and disappeared the day after an unruptured hydatid cyst was removed. Of 132 cases a rash occurred in 10 per cent,

¹ Tuffier. *Semaine méd.*, Paris, 1906, xxv, 121.

² Quénu. *Rev. de chir.*, Paris, 1910, xli, 241.

³ Stirling. *Intercol. Med. Journ. Australasia*, 1899, iv, 96.

⁴ Legg, W. *Trans. Path. Soc.*, Lond., 1874, xxv, 155.

⁵ Pheasants. *Bull. Johns Hopkins Hosp.*, Balt., 1909, xx, 292.

⁶ Dévé. *Bull. Soc. Anat.*, Paris, 1903, 6. s., v, 197.

⁷ Knaggs. *Trans. Clin. Soc.*, Lond., 1890, xxiii, 173.

⁸ McMurray. *Austral. Med. Gaz.*, 1896, xv, 185.

usually after operation (MacLaurin¹). It has been thought that urticaria is relatively less rare in children than in adults affected with hydatid disease.

As a rule, there is no change in the blood, but some cases shew eosinophilia. In some cases eosinophilia has been slight in degree and it is most exceptional to get such a high count as in Palazzo's² case (68.3 per cent) and in Augier's³ and in Seligmann and Dudgeon's⁴ cases, in which the percentage was 57. The occurrence of eosinophilia has no relation to a hydatid rash. After the cyst is opened the eosinophilia falls. In 10 cases examined by Ramsay⁵ there was eosinophilia in two only, 28.2 and 6.2 per cent respectively. In 2 of the 10 cases the cysts were suppurating, and, as might be expected from Opie's observations, there was no eosinophilia. Eosinophilia has a definite relation to the presence of animal parasites in the body, and has been thought to play a part in protecting against toxins manufactured by the parasites (Gulland⁶). If this is so, it should occur only when absorption of the contents of a hydatid cyst is going on, and this has been supported by the observation that it is almost always present when the cyst has ruptured into the peritoneum (Barling and Welsh⁷). Eosinophilia is by no means constant, and though its presence is in favour of the view that a doubtful tumour is a hydatid, its absence does not exclude this diagnosis. The blood-serum of patients with hydatid disease contains a specific precipitin (Fleig and Lisbonne⁸), which is thrown down if the blood-serum is mixed with a suitable hydatid fluid. Welsh and Chapman⁹ found this test to be positive in 9 cases of hydatid disease. A negative result is inconclusive, but a positive reaction is absolute proof of a hydatid (Welsh, Chapman, and Storey¹⁰). The reaction of fixation of the complement can also be employed (Laubry and Parvu¹¹).

The urine is normal unless there is some complication. A suppurating hydatid may by absorption lead to albuminuria or conceivably to albumosuria. The pressure of a large hydatid on the right renal vein may cause temporary albuminuria.

In Praetorius'¹² case albuminuria disappeared after incision and drainage of a hydatid cyst of the liver.

In very rare cases pressure on the inferior vena cava or on the renal veins has been thought to explain great diminution in the excretion of urine (Davis¹³). d/

¹ MacLaurin. *Austral. Med. Gaz.*, 1909, xxviii, 295.

² Palazzo. *Giorn. internaz. d. sc. med.*, Napoli, 1909, xxxi, 19.

³ Augier. *Journ. des sc. méd. de Lille*, 1908.

⁴ Seligmann and Dudgeon. *Lancet*, Lond., 1902, i, 1764.

⁵ Ramsay. *Intercol. med. Journ.*, 1906, xi, 380.

⁶ Gulland. *Brit. Med. Journ.*, 1902, i, 831.

⁷ Barling and Welsh. *Lancet*, Lond., 1910, ii, 1001.

⁸ Fleig et Lisbonne. *Compt. rend. Soc. Biol.*, Paris, 1907, lxii, 1198.

⁹ Welsh and Chapman. *Lancet*, Lond., 1908, i, 1338.

¹⁰ Welsh, Chapman, and Storey. *Ibid.*, 1909, i, 1103.

¹¹ Laubry et Parvu. *Bull. et mém. Soc. méd. des hôp. de Paris*, 1908, 3. s., xxvi, 391.

¹² Praetorius. *Berlin. klin. Wchnschr.*, 1898, xxxv, 312.

¹³ Davis. *Lancet*, Lond., 1900, ii, 1014.

^ /, but here again a negative result is not conclusive (HAHN). A stable antigen has been obtained from an alcoholic extract of the ~~cells~~ oocysts (Patterson and Williams).

x-rays.

A catapod, which is not a true Diaprosch, is also reported (Chauffard).

HAHN. München. med. Wochenschr., 1912, 1483

Patterson, G.W. and Williams, F.E. Journ. Path. and Bacteriol., Edin., 1924, xxvii, 1.

CHAUFFARD. Bull. Acad. de Méd., Paris, 1920, 3^e ser., LXXXIV, 160.

As an interesting coincidence Girard's¹ case of clubbed fingers associated with hydatid of the liver without any pulmonary changes may be mentioned.

To sum up: the physical signs of a hydatid cyst in the liver are out of proportion to the symptoms; there may be great enlargement with an absence of constitutional disturbance. The most marked clinical manifestations are produced when the cyst ruptures into adjacent organs or cavities, or suppurates—complications which will be described later.

DIAGNOSIS.—The diagnostic features are the presence of a cystic tumour in the liver which is considerably enlarged, and a marked absence of constitutional disturbance. The diagnosis cannot be made with absolute certainty unless fragments of the cyst or hooklets have been obtained by paracentesis or as the result of rupture of the cyst into the alimentary tract or in other positions. In the absence of this criterion the diagnosis is largely one of exclusion, and will be considered under the differential diagnosis.

Diagnosis of a Hydatid Cyst by Examination of Fluid drawn off by an Exploratory Puncture.—An exploratory puncture with a fine syringe should not be undertaken, inasmuch as very severe symptoms and even death may follow the escape of a small quantity of fluid into the peritoneal cavity. The characteristics of hydatid fluid from a living cyst are as follows: It is colourless, slightly opalescent, and neutral in reaction, with a specific gravity of 1002 to 1015, with about 1 per cent of solids. It contains mucin, but no albumin, small quantities of sugar, inosite, succinic acid, succinate of calcium, and sometimes traces of cholesterolin, leucine, and tyrosine. About half the total solid matter is chloride of sodium. According to Loeper² the fluid from a living cyst contains glycogen which rapidly changes into dextrose. Scolices and hooklets are not free in the living cysts and only become detached by paracentesis or when the parasite dies. The detection of hooklets is much facilitated by centrifuging the fluid; the scolices can be seen as small white dots by the naked eye. When the parasite dies, the fluid becomes albuminous and turbid, and a toxic body, comparable to mytilotoxin, may appear. When suppuration supervenes, the percentage of albumin of course increases. In the absence of hooklets, scolices, and membrane, it may be difficult to distinguish the hydatid fluid from that of some hydro-nephroses and from cerebrospinal fluid. The laminated membrane of the ectocyst may be discharged from a suppurating hydatid and a microscopic section presents a characteristic and beautiful appearance.

Differential Diagnosis.—A large number of conditions, such as tumours and cysts in or close to the liver, may imitate a hydatid cyst of the liver. A hydatid cyst may (I) project from the anterior surface of the liver, (II) be deeply seated in the substance of the organ, (III) project upwards towards the thorax, or (IV) downwards into the

¹ Girard. *Semaine méd.*, Paris, 1903, xxiii, 32.

² Loeper. *Clinique de l'Hôtel-Dieu de Paris*, 1906, v, 264.

abdomen. The conditions which may be confused with these four groups will now be considered seriatim.

(I) When the cyst projects from the anterior surface of the liver diagnosis is comparatively easy. There are, however, a number of conditions which may possibly be confused with it. *Simple cysts* of the liver, though rarely of such dimensions as to resemble a hydatid, cannot be accurately diagnosed until their contents or their walls are examined. In cystic disease of the liver the concomitant enlargement of the kidneys should suggest the true nature of the hepatic disease. In *malignant disease* there is usually cachexia, whereas in hydatid the general health is good. In addition, multiple malignant growths often are umbilicated, and there is generally pain, neither of which is present in uncomplicated hydatid disease. The distinction, however, may sometimes be very difficult.

Thus, Sargnon¹ describes a case in which hydatid was diagnosed and laparotomy performed; the liver, when exposed, presented the appearance of multiple growth, and the abdomen was accordingly closed; subsequently at the autopsy the growths were found to be multiple hydatid cysts. ←

Cholecystitis.—As a rule, inflammation of and about the gall-bladder does not suggest a hydatid cyst of the liver. It is only in the presence of a great deal of inflammatory adhesions around the gall-bladder and of the tongue-shaped elongation of the right lobe that difficulty is likely to arise. Pain is prominent in most cases of chronic cholecystitis, and rare in hydatid disease.

In a woman, aged fifty years, who was under my care the liver was much enlarged and extremely hard, but her general condition was so good that malignant disease seemed unlikely. She had been tapped without any result by a general practitioner. Laparotomy was performed, and a greatly thickened gall-bladder containing a large number of calculi found. The calculi were removed and the patient recovered. Microscopic examination of part of the wall of the gall-bladder removed at the operation only shewed chronic inflammation.

From Conditions in the Anterior Abdominal Wall.—Suppuration in the sheath of the rectus and in the anterior abdominal wall is more superficial than a hydatid, does not move with respiration in the same way, and may make the skin red and oedematous. Suppuration in the rectus is not common, and when it does occur, is usually below the umbilicus. A hydatid in the anterior abdominal wall is small and can be made out to be distinct from the liver and not to move with it. Phantom tumours and localised spasm of the right rectus abdominis muscle disappear gradually under an anaesthetic and are resonant on percussion. Localised paralysis of the rectus over the liver has been described by Potain² as resulting from rheumatism of the vertebral joints, in hysterical

¹ Sargnon. *Lyon méd.*, 1898, lxxxvii, 254.

² Potain. *Semaine méd.*, Paris, 1896, xvi, 209.

Renton reports a case in which hydatids were ^{found} at laparotomy
~~found~~ 5 years after an operation when carcinoma was
diagnosed.

J.M. Renton. Glasgow med. Journ., 1920, xciv, 311.

subjects, and in cardiac dilatation from local inflammation of the peritoneal covering of the liver; the bulging and local distension which result imitating a hydatid cyst of the liver.

(II) When the cyst is deeply embedded in the substance of the liver, especially in the posterior part of the right lobe, and expands and pushes the liver forwards, the diagnosis is more difficult. *Massive carcinoma* in the substance of the liver is accompanied by severe constitutional disturbance and cachexia, and runs a rapid course (*vide* p. 472). A *large cirrhotic liver*, when pushed forwards by flatulent distension of the stomach, may imitate enlargement due to a hydatid. In cirrhosis the enlargement is more uniform, affecting both lobes, and the surface is not perfectly smooth; other signs of cirrhosis may be present and the general health is not so good as in hydatid disease. *Gummatous enlargement* is usually painful, and would be accompanied by a positive Wassermann reaction. If any doubt exists, a course of iodide of potassium and mercury should be tried.

The *enlargement* due to lardaceous disease, leukaemia, and cardiac affections should be readily distinguished by signs of the primary diseases and examination of the urine, blood, and heart. Enlargement of the spleen would militate against ordinary, but not against multilocular, hydatid of the liver, and would be greatly in favour of lardaceous disease and leukaemia. The various forms of *suppuration in the liver*, such as a large tropical abscess, suppurative pylephlebitis, and cholangitis, are practically always accompanied by fever, often by rigors, and the constitutional disturbance is very considerable. The history of residence abroad, dysentery, appendicitis, or cholelithiasis would favour suppuration. But fever and constitutional symptoms are the points of most importance. Suppuration in a hydatid cyst of the liver is the same as a hepatic abscess, and it can only be diagnosed by a history of a cyst having existed in the liver for a considerable time. In *subphrenic abscess* the fever and constitutional disturbance, the history of acute onset, of symptoms pointing to gastric ulcer, and in some cases the presence of air (subphrenic pyopneumothorax), are sufficient to distinguish it from an ordinary hydatid cyst. A suppurating hydatid may by leakage set up a subphrenic abscess.

Aneurysm of the hepatic artery is very rare, and is nearly always accompanied by pain and jaundice, and the symptoms are only likely to resemble rupture of a hydatid cyst into one of the bile-duets.

(III) **Hydatid Cyst Projecting Upwards into the Thorax.**—When a hydatid cyst projects from the convexity of the right lobe, or in rare instances from the upper surface of the left lobe, it may be difficult to distinguish it from a pleural effusion, since it may displace the diaphragm upwards, lead to extensive collapse of the lung and to dulness over the greater part of the right side of the chest, without producing any downward displacement of the liver. In such cases the diagnosis may only be arrived at when the contents of the cyst are seen; for example, when rupture into the lung leads to expectoration of pieces of hydatid mem-

branc or when hooklets are found in fluid drawn off by an aspirator. Skiagraphy, by shewing the upward displacement of the diaphragm on the right side and its relation to the shadow cast by the heart, is more likely to assist in arriving at a correct diagnosis than any other means short of exploration at our disposal. When a hydatid cyst gives rise to the signs of a small pleural effusion and to considerable enlargement of the liver, the diagnosis is easier; but in a case with these signs the hepatic enlargement might be due to some other cause, such as cirrhosis, and the dulness in the chest to a small effusion. The dulness due to a pleural effusion differs somewhat from that of a hydatid cyst in the liver, which displaces the diaphragm upwards. If the line of dulness is highest in the axilla and falls somewhat both towards the spine and sternum, a pleural effusion is more probable; dulness at the base behind with a rounded summit is in favour of a cyst in the liver (Fowler and Godlee¹).

The diagnosis between a hydatid cyst in the upper and back part of the right lobe of the liver and one in the substance of the right lung, especially when near the base, is very difficult, as the clinical signs and symptoms are very much the same. There is said to be more cough in cases of pulmonary hydatid, and there may be a band of resonance below the dulness corresponding to the cyst, owing to the presence of some resonant lung below the hydatid. Haemoptysis may be an early symptom in hydatid of the lung, while it is not likely to occur with a hydatid of the liver except from extreme congestion of collapsed lung;² it is rare then, and would only occur late in the disease, when the diaphragm is displaced upwards to a marked degree, viz. to the level of the second rib or even of the clavicle. From constant pressure exerted by the cyst the diaphragm may atrophy so as to allow the hydatid to project into the pleural cavity or to communicate with the lung without any suppurative or ulcerative process.

What has been said about hydatids in the lung and the diagnosis from hydatid of the upper surface of the liver applies in the case of *hydatid of the pleural cavity*. As in the case of the lung, the question is more likely to arise on the right side. In Luff's³ case, however, a hydatid in the left pleura, containing six pints of fluid, gave rise to signs of hydatid of the liver with probable extension into the left pleura. It is impossible to distinguish betwixt a hydatid between the liver and diaphragm and a cyst projecting from the convexity of the liver. In both cases the liver is depressed and the pleural cavity encroached upon. A cyst between the layers of the suspensory ligament of the liver may have started in the superficial part of the liver and grown up out of it.

(IV) When the cyst projects downwards into the abdomen it is usually more readily recognised, but confusion may easily arise between it and other conditions, such as a dilated gall-bladder, renal tumour or

¹ Fowler and Godlee. *The Diseases of the Lungs*, p. 478, 1898.

² Galliard. *Arch. gén. de méd.*, Paris, 1890, clxv, 409.

³ Luff, A. P. *Lancet*, Lond., 1896, i, 1134.

displacement, and various other abdominal tumours. There is also the greater likelihood that cysts in this position may press upon the neighbouring viscera and thus complicate the diagnosis. A dilated gall-bladder may closely resemble a hydatid cyst hanging down from the under surface of the liver; usually, however, it is not so prominent, and there may have been attacks of biliary colic or of icterus in the past; though both these symptoms may follow rupture of a cyst into the bile-ducts. A dilated gall-bladder is pear-shaped and much more movable than a hydatid cyst. During a laparotomy a pendulous hydatid cyst arising near the gall-bladder may be mistaken for that viscus even by an experienced observer (*vide* p. 628). A hydatid cyst with local peritonitis may imitate calculous pericholecystitis (Longe¹).

Hydronephrosis of the right kidney when it passes forwards towards the abdominal wall may closely resemble a hydatid; for the colon need not necessarily lie in front of a large renal tumour. A hydronephrosis will project much more into the loin, the urine may be of a low specific gravity, and the occurrence of inflammation in the kidney or the transition of a hydronephrosis into a pyonephrosis would be shewn by pyuria. A copious discharge of urine associated with disappearance of the tumour is characteristic of an intermitting hydronephrosis. A soft *renal* or *suprarenal* growth on the right side may imitate a hydatid cyst projecting from the right lobe of the liver.

A man aged twenty-five had a fluctuating tumour below the liver, which was at first thought to be hydatid, but puncture only brought blood away. After death I found a large cystic endothelioma arising from the right suprarenal and invading the right lobe of the liver.

Renal and suprarenal growths probably move less on respiration than those connected with the liver, and tend to bulge into the loin; a bimanual examination should therefore always be made. A floating kidney might cause difficulty in diagnosis; Potain described a form of nephroptosis, "anteversion of the kidney," which is especially likely to resemble a hydatid of the liver unless a bimanual examination is insisted on.

Pancreatic and Peripancreatic Cysts.—Cysts in connexion with the pancreas or a collection of fluid in the lesser sac of the peritoneum (peripancreatic cyst) are usually more prominent towards the left, and are only likely to be confused with hydatid cysts attached to the left lobe of the liver. Pancreatic and other abdominal cysts and tumours should be separated from the liver by a zone of resonance, whereas a hydatid cyst should be continuous with it. Again, a pancreatic cyst is more deeply placed and should lie behind the stomach, while a hydatid cyst would be in front. In case of doubt the stomach should be inflated with air. In the following case a suppurating hydatid attached to the back of the left lobe of the liver imitated a pancreatic cyst:

¹ Longe. *Rev. de méd.*, Paris, 1910, xxx, 757.

A woman aged forty-nine, the mother of ten children, was admitted under my care at St. George's Hospital on November 30, 1901. Four months previously she suddenly had an attack of very severe pain accompanied by rigors and followed by jaundice. The attacks were repeated at intervals of about two weeks. The tumour was noticed after the first attack, and was thought to have varied in size from time to time. She was a fat woman with a large, tense tumour between the umbilicus and the ensiform cartilage; close to the latter it was dull on percussion, but elsewhere it was resonant; it could not be separated from the left lobe of the liver and did not bulge into the loin. This was important, since when asked a leading question the patient said it varied from time to time according to the amount of water, sometimes excessive, that she passed. There was no jaundice or bile in the urine. The diagnosis lay between a peripancreatic cyst, a hydronephrosis, and a hydatid cyst dependent from the left lobe of the liver. It was thought to be a peripancreatic effusion into the lesser sac of the peritoneum following pancreatitis, which possibly occurred as the result of the passage of gall-stones four months before. Accordingly on December 9 Mr. Sheild made an incision over the left linea semilunaris and came down on coils of intestines somewhat matted together; on separating them stinking pus with numerous daughter cysts welled up from a cyst attached to the left lobe of the liver. This cavity was drained. For a time the patient did well, but the discharge was very copious and she became very weak, eventually dying on December 21. At the necropsy there was a large subphrenic abscess between the diaphragm and the right lobe of the liver. In the left lobe of the liver there was a suppurating hydatid cyst which passed backwards and was adherent to the pancreas which appeared healthy. The liver was fatty, swollen, and weighed 7 pounds. The cystic and the common bile-ducts were much dilated, but there were no gall-stones in the gall-bladder. The spleen, 4 ounces, was healthy.

A large hydatid cyst should hardly be mistaken for *ascites* unless the cyst is so large that it almost fills the abdomen, and even then the dulness will not reach to the flanks. Chemical examination of fluid drawn off by a trocar will settle the question. A large ovarian cyst may resemble a pendulous hydatid cyst, especially one that has contracted adhesions to the lower part of the abdomen. The history of the tumour as indicating the situation where it was first noticed, whether near the liver or the pelvis, the connexion of the tumour with the liver or with the uterus, and vaginal examination may assist in making a diagnosis. An ovarian cyst under ordinary conditions will not move on respiration.

Duration and Prognosis.—It is difficult to estimate how long a hydatid cyst may remain alive and capable of active growth, but it may be twenty years.

A man aged thirty-five died in St. George's Hospital with a hydatid, the size of an adult's head, full of daughter cysts, in the right lobe; close to it there was a small, dried-up cyst. Nineteen years before he had been tapped, and presumably the small cyst had been then evacuated. Probably the two cysts were of the same age; but even if the larger cyst was due to infection at the time of tapping the other, it must have existed for nineteen years.

I have seen a large retroperitoneal got which clinically was indistinguishable from a hydatid.

As a rule the prognosis is
better in early than in
later life (DÉV.)
(as complications are
less likely to be present.)

The prognosis of a large hydatid cyst largely depends on whether it is operated upon or not. If not operated upon, it may die, shrivel up, and give rise to no further trouble, but a cyst which has remained quiescent or latent may suppurate without any manifest cause. Suppuration is a dangerous complication, and its possible incidence in the remote future must be faced in deciding not to call in surgical interference.

The size, rate of growth, and the possibility of rupture or suppuration supervening require consideration. If the cyst is sufficiently large to be diagnosed and is rapidly increasing in size, the danger of rupture is sufficient to make operation desirable. When a cyst gets smaller under observation, it may be undergoing spontaneous cure, and may be left alone without any immediate prospect of danger, but it is safer to remove it, for if suppuration supervenes, the conditions are then less favourable for successful operation. The situation of the cyst influences the prognosis: if it is deeply situated and in the upper and posterior part of the right lobe, it is both more likely to encroach on the thorax and more difficult to operate upon. Another important point which often cannot be determined is whether there is one cyst or whether they are multiple.

If a cyst is not growing rapidly, and is therefore not interfered with, there is the possible danger of traumatic rupture of the cyst, or of rupture into some viscus to which it has become adherent. Rupture always affects the prognosis and gives rise to anxiety, though the gravity of the prognosis varies according to the situation of the rupture. Thus, rupture into the pericardium is nearly always rapidly fatal. Duvé¹ has shewn that death is not inevitable when a cyst ruptures into the inferior vena cava, if the cysts discharged are few and small. Rupture into the peritoneum or even into the pleura may prove fatal very rapidly, and if the patient does survive, there is danger of peritonitis or of empyema. The effects of escape of hydatid fluid into the peritoneal cavity are considered on p. 413. Traumatic rupture of a living cyst may cause comparatively little disturbance, but rupture of a dead cyst, the contents of which have become toxic or infected, is most dangerous. Rupture into parts of the peritoneum cut off by adhesions is, of course, much less grave, but it may then be difficult to be sure that this has occurred. Gradual leakage into the general peritoneal cavity is not necessarily followed by severe symptoms. Rupture into the bile-ducts is very prone to cause suppurative cholangitis, and is therefore a grave complication. Ruptures into the lungs, alimentary tract, and externally are less serious. Cyr² estimated the mortality at 90 per cent when rupture occurred into the peritoneum, 80 per cent into the pleura, 70 per cent into the bile-ducts, 57 per cent into the bronchi, 40 per cent into the stomach, 15 per cent into the intestines, and 3 per cent on to the surface of the body. Suppuration also makes the outlook very gloomy. Some observers, especially in France, have noticed that pul-

1. Duvé. *Bull. Soc. Anat.*, Paris, 1903, 6. s., v, 185.

2 Cyr. Quoted by Hoppe-Seyler, Nothnagel's *Practical Encyclopedia*, "Diseases of the Liver," p. 802. English translation, 1903.

monary tuberculosis not uncommonly follows a hydatid cyst (Routier¹); but it is possible that the hydatid disease is really due to infection conveyed in the dietetic treatment of tuberculosis.

If the cyst is operated upon, the prognosis depends on the operation adopted, on complications arising from the operation, while there is, further, the possibility of there being other cysts which, though latent at the time of the operation and not then attracting attention, may subsequently give rise to trouble.

TREATMENT.—The treatment of hydatid cysts is essentially surgical, and consists in the evacuation or removal of the cyst. No drugs given by the mouth have any effect on the parasite. A number of different methods have been employed.

I. Simple **puncture with a trocar** and removal of some or all of the fluid contents of the cyst. This method, which is the oldest, has been much employed, and has naturally met with approval, as it is simple and easy to perform. After the withdrawal of the fluid the parasite, under favourable conditions, dies and the cyst shrivels up. Though in many cases cure results from simple tapping, there is an element of risk, since severe symptoms and even death have followed this simple operation. Dieulafoy² considers that the bad effects of simple tapping are due to the cyst having been only partially evacuated, and that as a result some of the residual fluid has escaped into the peritoneal cavity; he, therefore, insists on complete evacuation of the cysts, and directs that an aspirator should be used. The safe course, however, is to have the cyst fully exposed by a surgeon and then treated as the details of the case, thus plainly seen, shew to be the proper course. Simple puncture may also be followed by suppuration.

II. A modification, or rather an addition to the simple procedure of tapping, consists in the injection of antiseptic fluids into the interior of the cyst. In this method a little of the fluid is removed by means of a small puncture, and a small quantity of some fluid is then introduced with the object of killing the parasite. This method, advocated by Baccelli, was successfully practised by Bókay,³ who injected a solution of perchloride of mercury 1 in 1000. Other fluids, such as ox-bile, so as to imitate one supposed cause of spontaneous cure, iodine solution, carbolic acid, alcohol, formaline, have been used with the same object. These methods are dangerous and are only mentioned to be avoided. Suppuration, and even fatal mercurial poisoning, have been recorded.

III. **Acu-puncture.**—The insertion into the cyst of long needles which are withdrawn after about a quarter of an hour. This probably acts by allowing the cyst to leak into the peritoneum. It is a dangerous practice.

IV. **Electrolysis.**—Hilton Fagge and Durham⁴ employed this method

¹ Routier. *Bull. et mém. Soc. chir. de Paris*, 1909, xxxv, 3.

² Dieulafoy. *Bull. Acad. de méd., Par.*, 1899, 3. s., xli, 530.

³ Bókay. *Arch. f. Kinderh.*, 1897, xxiii, 310.

⁴ *Med.-Chir. Trans.*, Lond., 1871, liv, 1.

DÉVÉ described a case in which
a cyst was punctured, 26 days
later it was operated upon & death
rapidly followed. It was thought to be
due to anaphylaxis.

DÉVÉ. Compt. rend. Soc. Biol., Par., 1910, LXIX

with success in 7 or 8 cases. It consisted in introducing two needles into the cyst and then passing a constant current through the cyst, the needles being attached to the negative pole, while the positive pole of the battery was connected with a sponge placed on the skin of the abdomen over the cyst. Electrolysis acts in the same way as simple acu-puncture, and not, as was at first imagined, by decomposition of the fluid in the cyst.

Accidents and Bad Effects following Simple Tapping.—When a hydatid cyst is tapped and the fluid is partially drawn off, some of the residual fluid not uncommonly escapes into the peritoneal cavity, and its presence may be shewn by some shifting dullness and fluctuation in the flanks and lower part of the abdomen. There are usually no bad symptoms, but intense itching followed by urticaria lasting a few hours to two days may result; sometimes peritonismus, or signs of false peritonitis, follows tapping, and in rare cases death preceded by convulsions and collapse has occurred. The fluid in a living hydatid cyst does not contain albumin or hooklets, does not produce toxic effects when injected into animals, and is usually without any bad effects on man (Kirmisson, Kornach, Martini, Maury, Boinet and Chazoulière).

Chauffard,¹ however, met with a most exceptional case in a man aged thirty-five years; a hydatid cyst was punctured and 10 c.c. of clear fluid drawn off; epileptic convulsions set in and death followed within twenty-five minutes from the time of puncture of the cyst. The cyst contained clear fluid which was without any poisonous action on animals. *A*

When the hydatid cyst dies and undergoes aseptic necrosis without the introduction of micro-organisms, the characters of the fluid, both physical and physiological, change. The fluid becomes turbid, yellow, syrupy, contains hooklets, albumin, and a toxic body which is analogous to mytilotoxin found in the livers of poisonous mussels, and gives rise to the urticaria and other symptoms sometimes manifested after the escape of hydatid fluid into the tissues. This poison has been found by Boinet and Chazoulière² to crystallise in long, silky needles. Physiologically when injected into animals it induces convulsions, loss of motor and sensory power, followed by slowing of the heart, rapid respirations, dilated pupils, fall of blood-pressure, prostration and collapse, and in larger doses death. Viron³ found a toxin in hydatid fluid from sheep which produced acute inflammation of the tissues.

In a man aged twenty-three years with jaundice, dangerous collapse followed exploratory paracentesis of a hydatid cyst, and subsequently profuse urticaria appeared on the abdomen, legs, and extensor surfaces of the arms, and lasted for some hours (L. Humphry⁴). Two weeks later $\frac{1}{50}$ grain of atropine was injected to prevent recurrence of these severe symptoms and paracentesis was

¹ Chauffard. *Semaine méd.*, Paris, 1896, xvi, 265.

² Boinet et Chazoulière. *Rev. de méd.*, Paris, 1898, xviii, 845.

³ Viron. *Arch. de méd. expér. et d'anat. path.*, Paris, 1892, iv, 136.

⁴ Humphry. *Lancet*, 1887, i, 120.

successfully performed. Injection of the fluid into guinea-pigs and a dog caused marked toxic symptoms. Bryant¹ recorded sudden death five minutes after paracentesis of hydatid of the liver; the trocar passed through the portal vein, and it is possible that the hydatid fluid entered directly into the circulation.

The bad effects of hydatid fluid are probably due to anaphylaxis or hypersensitiveness, and are ~~comparable to those produced by the injection of a foreign protein or serum.~~ The symptoms may be grouped under three headings: (a) Cutaneous—pruritus and urticaria; (b) Cerebrospinal—epileptiform convulsions; and (c) collapse and cardiac failure.

As mentioned above, a hydatid rash has in very rare instances been seen without rupture or leakage of the cyst²; usually it is due to one or other of these events. It has been produced by contact with the fluid, as in the case referred to by Achard of two individuals who suffered from urticaria after making a necropsy on a case of hydatid cyst. Fatal toxic symptoms supervened five days after abdominal operation and drainage of a hydatid cyst in a case recorded by Fuster and Godlewski. A trocar has also been known to wound a large branch of the portal or hepatic vein and induce fatal haemorrhage. Puncture may be followed by suppuration in the cyst, and thus not only is time lost, but a dangerous complication results.

Surgical Treatment.—As already pointed out, the more satisfactory method of dealing with hydatid cysts of the liver is by surgical means, the abdomen being opened and the cyst exposed. For the various methods of dealing with the cyst the reader should refer to a surgical textbook. In a few instances the whole of the cyst, including the external adventitious capsule, has been removed. Generally the incision of the cyst and the removal of the parasite and daughter cysts are performed. There are dangers connected with the operation, of course, such as haemorrhage from veins in the capsule of the cyst, and extensive and prolonged leakage of bile due to free communications between the cyst and the larger bile-ducts. The loss of bile from a cyst, if continued, may lead to emaciation if it is so extensive that all or nearly all the bile escapes from the body by this channel. This result need not occur if a fair proportion of the bile enters the duodenum. As a possible danger due to the operation, amyloid / long-continued suppuration leading to ~~lardaceous~~ disease may be mentioned, but is much less likely to occur now than in former times.

Prophylaxis.—Raw vegetables should be carefully washed, so as to prevent the possibility of ova being conveyed by them. As the ova are almost entirely derived from the faeces of dogs, care must be taken by those who keep dogs in the house. In places where hydatid disease is frequent, drinking-water, one of the chief means by which the disease is spread, should be filtered or boiled, and fruit and vegetables should not be eaten unless boiled or washed with filtered or boiled water.

¹ Bryant, T. *Trans. Clin. Soc.*, 1876, xi, 230.

² McMurray. *Australian Med. Gaz.*, 1896, xv, 185.

1 | due to the interaction of echinococcal
protein and its anti-bodies, the symptoms are therefore
comparable to those seen in serum disease.

X-ray Treatment.

Arce's observations go to show that deep x-ray therapy
kills the parasite and so may enable small cysts to become
obsolescent, and render safer operative treatment of large cysts.

ARCE, J. Bull. Acad. de Méd., Paris, 1924, 3^e ser., CXII, 1290.

occurs in
about 14 per cent
^{in adults or 7 per cent in children}
of the cases (DÉVÉ);
this is based on the
percentage of cases in
which multiple hydatids
of the peritoneum are
combined with hepatic
hydatid.

DÉVÉ. Journ. med. franc., Paris,
1910, IV, 525; and
Arch. de méd. des enf., Paris, 19
XXI, 225.

Legislation should make it obligatory on the officials of slaughter-houses to burn the offal of sheep and oxen infected with hydatid cysts, and to prevent dogs getting access to this source of infection. Strict measures of this kind should be employed to stamp out the disease and prevent it obtaining a foothold in countries like America, where as yet it is not widespread. Another beneficial measure would be the destruction of stray and homeless dogs.

Complications.—The chief complications are rupture and suppuration of the cyst.

Rupture may occur into the peritoneum, into adjacent hollow viscera, or after perforation of the diaphragm, into the pleura, lung, or pericardium. In order to open into the serous cavities on the other side of the diaphragm the cyst must first become adherent to the under surface of the diaphragm and then penetrate the muscular and serous coats, just as a cyst has to work its way through the coats of the stomach or intestine to rupture into these organs. The process of perforation depends on atrophy, from constant pressure, of the tissues of the diaphragm or intestine, which have become adherent to the cyst by local adhesive peritonitis. Suppuration renders perforation and rupture much easier, and in rare instances a suppurating cyst may perforate the abdominal wall.

Rupture into the peritoneal cavity may be divided into two categories:

(a) Into the general peritoneal cavity; the cyst may rupture freely or merely leak. (b) Rupture into a localised part of the abdominal cavity which has been cut off by previous local peritonitis. A localised or subphrenic abscess may thus result.

Rupture of a hydatid cyst into the peritoneal cavity ~~apart from trauma or suppuration is rare, and, as already pointed out, is more readily produced in a suppurating cyst.~~ A hydatid cyst which is not suppurating may rupture as the result of direct or indirect violence, or even spontaneously without any manifest cause. It has been known to occur in pregnancy and may possibly be precipitated by increased intra-abdominal pressure. Usually, however, there is a history of a blow on the abdomen immediately preceding the onset of pain and collapse.

The escape of hydatid fluid into the general cavity of the peritoneum may be rapidly followed by either (i) very severe symptoms of collapse succeeded by fatal syncope or by peritonitis, or (ii) comparatively trivial symptoms. The factor which determines whether severe or comparatively trivial symptoms follow the escape of hydatid fluid into the peritoneal cavity is probably the character of the contents of the cyst. If the parasite is dead, the fluid becomes toxic, whereas the fluid from a living cyst is harmless. Rupture of a suppurating cyst, or of one in connexion with an infected bile-duct, into the peritoneal cavity naturally sets up acute peritonitis. The sudden acute symptoms might, in the event of the presence of a hydatid cyst in the abdomen being unknown, be mistaken for irritant poisoning or perforation of an abdominal viscus. In the absence of an urticarial rash the real nature of the condition

would probably only appear when the abdomen was opened. The following case illustrates the occurrence of death from peritonitis and the danger that attaches to postponing operative interference :

A woman aged thirty-four had a swelling in the upper part of the abdomen for thirteen years; it began in the epigastrium and gradually enlarged. She was admitted into St. George's Hospital on October 19, 1893, and a large hydatid was diagnosed. Operation was advised, but she was alarmed and left the hospital, only to return five days later in collapse with urticaria; the tumour could no longer be felt. Mr. Turner performed laparotomy and found a ruptured hydatid cyst which occupied the whole of the left lobe of the liver. The patient died next day. There was general peritonitis. No other hydatid cysts were found in the viscera.

The leakage of a cyst into the peritoneal cavity may give rise to collapse and symptoms suggesting intestinal obstruction (peritonismus). The rupture is accompanied by sudden pain, but if the contents are not toxic or infective, recovery may follow with or without the significant, but comparatively trivial, incident of an urticarial eruption (*vide* p. 403). Eosinophilia appears to be almost constant (Barling and Welsh¹). Rupture of a large cyst may cause considerable ascites which lasts for some time and reaccumulates after tapping. Debove and Soupault² described such a case in which tuberculous peritonitis was diagnosed. The rupture may be complicated by the escape of bile into the abdominal cavity (choleperitoneum). The communication of the cyst with the bile-duct may take place before or after the rupture of the cyst into the peritoneum; Dévé³ believes that the latter is most often the case and compares it to the escape of bile into a cyst after tapping. ~~The effusion of bile does not necessarily set up peritonitis.~~ When the bile is sterile and there is no peritonitis, the abdomen gradually swells, and after days or weeks requires tapping; the effusion has a great tendency to recur. ~~It is curious that there is no jaundice, for the peritoneum has great powers of absorption and the quantity of bile in these cases is often considerable.~~

Two remote effects of rupture of a hydatid cyst into the peritoneum are: (I) infection of the peritoneum with daughter cysts; and (II) echinococcic pseudo-tuberculosis of the peritoneum.

Secondary infection of the peritoneum with numerous daughter cysts may eventually cause considerable trouble. Doubt has been thrown on the secondary infection of the peritoneum with daughter cysts from rupture of a hydatid cyst of the liver, and it has been suggested that what appear to be secondary implantations are really independent cysts,⁴ but this is not in accordance with the clinical facts that some years after rupture of a hydatid cyst in the liver other cysts may be found scattered over the peritoneum. The favourite situations for these secondary cysts

¹ Barling and Welsh. *Lancet*, Lond., 1910, ii, 1001.

² Debove et Soupault. *Bull. et mém. Soc. méd. des hôp. de Paris*, 1892, 3. s., ix, 855.

³ Dévé. *Rev. de chir.*, Paris, 1902, xxvi, 67; 1913, xxxvii, 125.

⁴ Potherat. *Bull. et mém. Soc. de chir. de Paris*, 1900, xxvi, 54.

In 1918 DÉVÉ referred to 69 cases of hydated choleperitoneum, and gave a detailed description of the membrane that lines the cavity occupied by the bilious effusion; it is composed of organising granulation tissue and contains crystals of bilirubin.

multiple young cysts } A
may imitate free
condition.

are the great omentum and the pelvis. It probably takes about two years for the cysts to develop sufficiently to give rise to signs or symptoms. It is somewhat remarkable that secondary infection of the peritoneum with daughter cysts may occur in cases in which the original cyst has been in communication with a bile-duct and the daughter cysts exposed to the action of the bile.

Dévé¹ has seen secondary cysts develop in the peritoneum in cases with a bile-stained peritoneal effusion due to rupture of a hydatid cyst, already in communication with a bile-duct, into the peritoneal cavity. He found that scolices ~~still continued to grow~~ in a mixture of equal parts of hydatid fluid and bile. /e

Pseudo-tuberculosis of the peritoneum² after rupture or leakage of a hydatid cyst is a rarely recognised though interesting condition. It consists in small granulomas covered over by the endothelium of the peritoneum and containing pieces of hydatid membrane or hooklets. Histologically there are giant, endothelioid, and small round cells. The process may be regarded as an attempt to absorb the bits of membrane and the hooklets. A

Rupture into the pleura of course usually occurs on the right side. The effusion into the pleura may be clear or may become purulent; in the latter event the pleural cavity may be much like a large suppurating hydatid cyst with numerous daughter cysts floating on it. Such an empyema may burst into the lung, and I have known suffocation result. If, as fortunately usually happens, the patient survives, a pyopneumothorax or a broncho-biliary fistula may result. Rupture of a hydatid cyst into the pleura may lead to an extravasation of bile into the pleural cavity; Dévé³ quotes two such cases recorded by Cruveilhier and Douart.

Rupture into the Lung.—If the lower part of the pleural cavity is obliterated by adhesions and the cyst perforates the diaphragm, rupture into the lung may follow and set up a pneumonic or even a gangrenous condition in the neighbourhood. The hydatid fluid may pass into the lung and give rise to serious dyspnoea, and hydatid membranes, which may be bile-stained, may be coughed up. Impaction of the membranes or daughter cysts in the bronchi or trachea may give rise to suffocative dyspnoea. When a hydatid cyst freely communicates with a bronchus, bile may pass into the lung and a broncho-biliary fistula may result. Out of 45 cases of broncho-biliary fistula collected by Graham⁴ 10 were due to hydatid cysts of the liver. These fistulous communications between the lung and hydatid cysts are more likely to occur when the hydatid projects from the convexity of the liver. Dévé⁵ has collected 11 cases in which the cyst became gaseous after rupture. A | Burgess

¹ Dévé. *Compt. rend. Soc. Biol.*, Paris, 1903, lv, 75. l.c

² Vide Dévé. *Rev. de chir.*, 1902, xxvi, 79; *Arch. de méd. expér. et d'anat. path.*, Paris, 1907, xix, 347.

³ Dévé. *Rev. de chir.*, Paris, 1902, xxvi, 67.

⁴ Graham, J. E. *Trans. Assoc. Am. Phys.*, 1897, xii, 247.

⁵ Dévé. *Rev. de chir.*, Paris, 1907, xxxv, 549.

Burgess. *Brit. Journ. Surg.*, 1921, ix, 253.

Jones¹ recorded rupture of a suppurating hydatid of the liver into a bronchus in a girl aged eight years. The chest wall was incised and the cyst eventually extracted from the lung; recovery followed.

Rupture into the pericardium is very rare, and is fatal either directly from shock or later from pericarditis.

Rupture into the Bile-ducts.—The frequency with which this occurs is difficult to estimate, for it often gives rise to no clinical manifestations, or may be mistaken for biliary colic due to gall-stones. When the communication between the cyst and the bile-duct is small, the fluid in the

cyst may run quietly away and the cyst may shrivel up; on the other hand, the cyst may be infected from the bile-duct and suppurate. The characteristic cases are those in which the communication between the cyst and the duct is sufficiently large to allow daughter cysts to escape into the duct and pass along its lumen. This gives rise to biliary obstruction, jaundice, colic, and may easily be regarded as due to gall-stones. In some cases there is fever from infective or suppurative cholangitis. Fragments of cysts or hooklets have, in rare cases, been found in the vomit, but are more often detected in the stools. The cysts

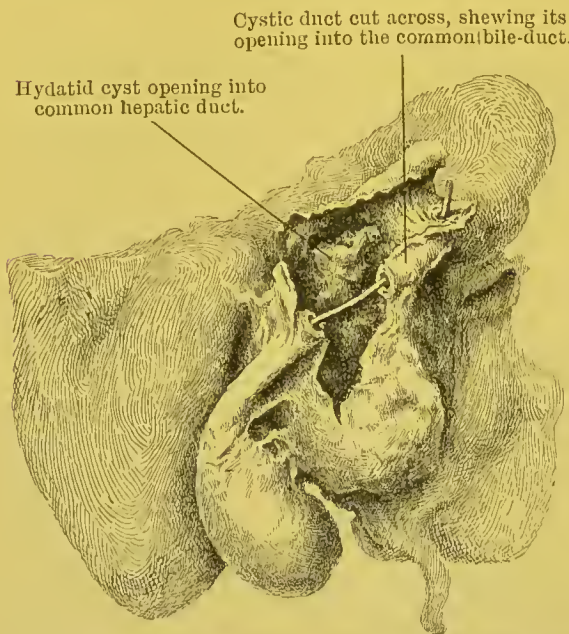


FIG. 53.—The common hepatic duct greatly dilated from the presence of part of a hydatid cyst which has ruptured into it. The cystic duct has been cut across so as not to obscure the view. From a specimen (Series IX, 196A) in St. George's Hospital Museum. (Drawn by Dr. E. A. Wilson.)

may remain in the ducts and cause considerable biliary obstruction and dilatation of the ducts. Possibly the hydatid fluid may, in the first instance, irritate the mucous membrane, in virtue of toxic bodies formed in the dead cysts, and set up a descending cholangitis. But in most cases cholangitis is due to infection, very possibly ascending from the duodenum, which is favoured by the presence of the grape-skin-like membranes in the larger bile-ducts. Cholangitis may spread into the evacuated cyst and cause suppuration. The suppurating cyst or ducts may perforate or leak into the peritoneal cavity and give rise to acute peritonitis or a localised subphrenic abscess. The hydatid membranes may remain impacted in the common bile-duct or even in the hepatic duct of one lobe of the liver.

¹ Jones. *Lancet*, Lond., 1899, ii, 1435.

It occurs equally on the two sides (DEVE)

OLIANO could only
collect 11 cases operated
upon.

Stagnation
from

as a more coincidence with
hydrated disease of the liver;
be due to pressure exerted on
by a cyst on biliary ducts, or be
secondary to cholecystitis caused
by rupture into gall bladder
(Désé) or to ~~cholecystitis~~

OLIANI. Polichin, Rome, 1919, XXVI, sez. chir., 177

DÉVÉ Compt. rend. Soc. de biol., Paris,
1919, LXXVIII, 419

In a case under my care it seemed probable that they had for a considerable time remained in the left hepatic duct and shortly before death moved into the common duct, for the ducts in the left lobe which contained a small cyst were all dilated and suppurating, while those in the right lobe were normal.

When in the common bile-duct the membranes may project into the duodenum through the biliary papilla and pass into the intestine or they may remain in the duct. The cyst may, after rupturing into the bile-duct, perforate the diaphragm and so give rise to a broncho-biliary fistula.

Sudden death from rupture of a hydatid cyst into the left hepatic duct occurred in a man aged forty-four, and was explained by Gouraud and Rathery¹ as due to absorption of the hydatid fluid by the intestines. This exceptional result is comparable with sudden death from rupture of a hydatid cyst into the peritoneal cavity (*vide* p. 415).

The symptoms of colic followed by jaundice so strongly suggest gall-stones that the true state of affairs is not likely to be suspected unless the existence of a hydatid cyst has previously been recognised, and unfortunately hydatid cysts in the portal fissure or Spigelian lobe, positions which favour rupture into the ducts, are specially difficult to diagnose. The condition cannot be diagnosed unless pieces of bile-stained hydatid membrane are found in the faeces or in the vomit. [^] Calculi may coexist with hydatid cysts in the bile ducts and be secondary to cholangitis set up by the rupture of the cyst into the duct (Terrier,² Hinder³). [^] The bile-staining of hydatid membranes is in favour of their having passed down the ducts, but is not absolutely pathognomonic, for a cyst already in connexion with a bile-duct might discharge into the stomach or bowel. When suppurative cholangitis has supervened, the underlying cause may be thought to be cholelithiasis, or the fever, rigors, and jaundice might be referred to pylephlebitis; but pain and jaundice are less frequent in suppurative pylephlebitis than after rupture of a hydatid into the bile-ducts.

(Calculi due to hydatid rupture are twice as frequent in men as in women) (DEVE)

As the diagnosis is difficult and is usually made on the post-mortem table, the number of reliable published cases of passage of hydatid cysts by the bile-ducts in which recovery has occurred is comparatively small. I have notes of nine cases in which complete recovery followed. Cyr estimated the mortality at 70 per cent. It is probable that as more cases of jaundice due to obstruction of the larger ducts are now operated upon, more examples of the collapsed cysts obstructing the bile-ducts will be forthcoming.

Stirling⁴ published a case which recovered after cholecystotomy and the subsequent discharge of hydatid membrane from the wound. The first symptom

¹ Gouraud et Rathery. *Bull. Soc. Anat.*, Paris, 1900, 6. s., ii, 307.

² Terrier. *Bull. et mém. Soc. de chir. de Paris*, 1906, xxxii, 848.

³ Hinder. *Trans. viii. Australasian Congress*, 1909, i, 317.

⁴ Stirling. *Intercolonial Med. Journ. Australasia*, 1899, iv, 98.

—pain like biliary colic—came on suddenly nine days before the operation, and was followed by jaundice and rigors. In a woman aged forty, operated upon by F. T. Stewart,¹ the hepatic and common bile-ducts contained hydatid cysts, while the gall-bladder contained both gall-stones and free hydatid cysts. It is probable that the previous passage of gall-stones through the cystic duct had dilated the duct and thus enabled the cysts to pass out of the common hepatic duct through the cystic duct into the gall-bladder. Under ordinary conditions hydatid membranes would never be able to work their way up a normal cystic duct.

Persistent discharge of bile from the wound after operation on a hydatid cyst may be due to impaction of a daughter cyst in the common bile-duct.

Rupture into the stomach is rare, and is more likely to occur when the cyst is in the left lobe of the liver. Of 11 cases referred to by Davaine, 6 were fatal. When rupture has taken place, the cyst may become tympanitic from the entry of air, and pieces of hydatid membrane, which may be bile-stained, may be recognised in the vomit or in the faeces.

Rupture into the intestines is also rare. The prognosis seems to be better than when rupture occurs into other hollow viscera, for of 15 of Davaine's² cases only one died. Rupture into the duodenum is very rare, and an exact diagnosis during life is hardly possible.

In a case reported by Hale White³ a hydatid in the left lobe was opened during life, the patient eventually died, and a second, suppurating, hydatid cyst was found in the right lobe. The cyst in the left lobe communicated by a rather long passage with the duodenum. In a man aged twenty-six years who died jaundiced and emaciated there were two cysts, one containing bile which was opened during life. After death a large hydatid cyst, which had opened into the duodenum, was found in the right lobe.⁴

When rupture into the colon occurs, the prognosis would seem to be very good, since in 21 cases collected by Letanneur⁵ no deaths took place. On the other hand, the diagnosis of these cases, unless confirmed by necropsy, is open to doubt; some of them may be cases of rupture into the bile-ducts.

Rupture into the inferior vena cava or the hepatic veins is very rare. Of 11 cases collected by Dévé⁶ the cyst opened in 7 into the inferior vena cava, and in 4 into the hepatic veins. In 8 of these cases death occurred very rapidly; this may be due to impaction of cysts in the right side of the heart or to pulmonary embolism; but in some cases there is no evidence of embolism and death may have been due to toxic bodies in the hydatid fluid. Rupture into these veins need not necessarily give

¹ Stewart. *Phila. Med. Journ.*, 1899, iv, 433.

² Davaine. *Traité des Entozoaires*, Paris, 1877.

³ Hale White. *Trans. Path. Soc.*, 1885, xxxvi, 252.

⁴ *St. Barth. Hosp. Rep.*, 1899, xxxv, Registrar's Report, p. 214.

⁵ Letanneur. Quoted by Potain, *Journ. de méd. et chir.*, Sept. 10, 1900.

⁶ Dévé. *Bull. Soc. Anat.*, Paris, 1903, 6. s., v, 185.

Suppuration is more often seen
in older patients than in
the young; Vegas and Gransell
found that suppuration occurred
in 14 per cent of the cases in
adults and 6 per cent in children.

Chauffard. Bull. Acad. de méd., Paris
1920, 3^e sér., LXXIV, 160.

rise to sudden death if the daughter cysts discharged into the blood-stream are few and quite small.

There is a specimen (No. 1371) in the Museum of the London Hospital of rupture of a hydatid cyst in the right lobe of the liver into the inferior vena cava.

In very rare cases (Seidel, Vegas and Cranwell¹) fatal pulmonary embolism has been due to thrombosis of the inferior vena cava, set up by compression of the vein by a cyst. In most exceptional instances a hydatid cyst has ruptured into the pelvis of the kidney, the gall-bladder, or the portal vein. Rupture through the abdominal wall is practically unknown, as a cyst would now be treated surgically long before it had penetrated the abdominal wall. It is the most favourable place for spontaneous rupture; of 21 cases collected by Murchison, 13 recovered.

Suppuration in a hydatid is a serious complication, as it converts the case into one of hepatic abscess. The symptoms are much the same in both cases, but in hydatid there is a marked tendency to perforate or rupture into adjacent organs or cavities; but since adhesions are less frequent around ordinary hydatid cysts, a suppurating one is not so likely to point through the skin as an ordinary hepatic abscess.

Mechanism of Suppuration in a Hydatid Cyst.—Suppuration may be set up in several ways: It may be due to direct infection from without after paracentesis or incision. It may be due to rupture of the cyst into the ducts, or may follow injury to the liver. In the latter instance the resistance of the tissues around the cyst is so reduced that any micro-organisms in the neighbourhood are able to multiply and set up inflammation. Suppuration may be due to infection of the liver itself or of the bile-ducts.

In a woman successfully operated upon in St. George's Hospital by Mr. L. Jones for gall-stones in the gall-bladder and common duct, there supervened, after an interval of six weeks' normal temperature, suppuration in a small hydatid cyst previously latent.

Petit² has described the spread of infection from the pleura, but in most cases of associated empyema and suppurating hydatid cysts the pleura is secondarily involved. Suppuration may occur as the result of haemic infections; for example, in enteric fever, infective endocarditis,³ and the puerperal state. When there are several cysts in the liver, suppuration may be confined to one or may extend to the others.³ A suppurating mother-cyst may contain daughter cysts which are not purulent. Suppuration has occurred in a cyst which appeared to have undergone spontaneous cure.

1) influenza,
(Chauffard)

1) calcified

(Chauffard).

The results of bacteriological examination of suppurating hydatid cysts are somewhat divergent. In some instances no micro-organisms have been found, and it has been suggested that suppuration is due to

¹ Quoted by Dévé. *Bull. Soc. Anat.*, Paris, 1903, 6. s., v, 196.

² Petit. *Rev. mens. de méd. et de chir.*, 1877, i, 678.

³ For illustrative case *vide* Sinclair White, *Brit. Med. Journ.*, 1897, ii, 398.

chemical poisons (Chauffard and Widal¹); and, as already mentioned, Viron² found a toxin in the hydatid fluid from a sheep which set up acute inflammation. But it is more probable that the organisms have died out. In some cases, streptococci, *Staphylococcus pyogenes aureus* and *citreus*, pneumococcus, and *Bacillus coli* have been isolated in pure or mixed cultures. The extremely fetid character of the pus may depend on the presence of anacrobic micro-organisms.

In a fetid but not gaseous suppurating hydatid cyst in a boy aged eleven years Hallé and Bacaloglu³ found, in addition to *B. coli* and streptococci, two strictly anaerobic microbes—*Staphylococcus parvulus* and *Bacillus fragilis*.

Haemorrhage into a suppurating hydatid cyst is not uncommon, and as a result the contents have a dark purplish-red colour not unlike that in tropical abscess. Production of gas in a suppurating hydatid cyst is very rare; this may be due to the *Bacillus aerogenes capsulatus* or to other anaerobic organisms. (Garnier⁴ described *Bacillus moniliformis* in a gaseous suppurating hydatid. Such as) The physical signs are an amphoric note on percussion and a bell note over the cyst. Suppurating gaseous hydatid cysts (pyopneumohydatid) have been recorded by Habershon,⁵ Lippmann,⁶ Gilbert and Weil,⁷ Griffon.⁸ In 1907 Dévé⁹ collected 24 examples of gaseous suppurating hydatid cysts in the liver, which had no communication with the lungs, intestines, or exterior.

A suppurating hydatid cyst by leaking may give rise to a subphrenic abscess, or exceptionally to a subphrenic pyopneumothorax.

Tuffier and Barbarin¹⁰ described the case of a woman who was operated upon for a gaseous subphrenic abscess on the right side, which displaced the liver backwards. After death it was found that this depended on a suppurating hydatid cyst which had also set up general peritonitis.

For the general clinical features of suppurating hydatid cysts the reader should refer to the description of hepatic abscess.

ALVEOLAR HYDATID

Synonym: Multilocular Hydatid.

History.—Cases of this rare disease were formerly regarded as examples of colloid carcinoma of the liver, until Virchow, in 1856, demonstrated their parasitic nature.

¹ Chauffard et Widal. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1891, 3. s., viii, 168.

² Viron. *Arch. de méd. expér. et d'anat. path.*, Paris, 1892, iv, 136.

³ Hallé et Bacaloglu. *Ibid.*, 1900, xii, 689. ⁴ Garnier. *Ibid.*, 1907, xix, 785.

⁵ Habershon, S. H. *Practitioner*, 1902, lxviii, 178.

⁶ Lippmann. *Compt. rend. Soc. Biol.*, Paris, 1902, liv, 218.

⁷ Gilbert et Weil. *Ibid.*, 1898, l, 657.

⁸ Griffon. *Clinique médicale de l'Hôtel-Dieu*, Paris, 1906, v, 67.

⁹ Dévé. *Rev. de chir.*, Paris, 1907, xxxv, 529.

¹⁰ Tuffier et Barbarin. *Bull. Soc. Anat.*, Paris, 1898, lxxiv, 689.

Adam Gaz. d. hôp. 1913, LXXXVI, 37
refers to 2 more cases in
France & says it has
spread into the Swiss
Nest. Congress of Pathology, Oct 1912
gives the subject - look up.

Col Skinner April 27 found out
that specimens at Nelly
were burned

It has spread into the
Jura, and at least 4
cases have been described
in this part of France
(Adam; Martin and Tissot)

Adam, F. Gaz. d. hôp. de Paris, 1913, LXXXVI, 37
Martin et Tissot. Ann. de méd. de l'ass., 1922, III

Incidence.—The disease is very rare, though possibly it is occasionally overlooked or regarded as malignant disease or multiple hydatids of the ordinary kind. In 1901 Melnikow-Raswedenkow¹ collected 235 cases. It is met with in the south of Germany, Bavaria and Würtemberg, Hanover, Switzerland, Austria, and, according to Posselt,² in the Tyrol. Dicaulfoy³ was only able to refer to two cases of alveolar hydatid-disease in France—one of the liver (Bruyant⁴), the other of the lung and pleura (Rénou⁵). It was formerly regarded as rare in Russia, but in 1901 70 cases were collected by Melnikow-Raswedenkow, who considers that it is more often met with there than elsewhere. It is generally stated that no case has been recognised in England. The ~~few~~ specimens of this disease in the Army Medical Museum at Netley (Nos. 1230, 1239) have been destroyed.

Hilton Fagge⁶ examined a specimen of colloid cancer in the museum of Guy's Hospital which Frerichs had suggested might be alveolar hydatid, but found nothing to support this view.

In America 6 cases have been reported, chiefly in Germans (Osler⁷). Its geographical distribution differs from that of the common echinococcus, and it is noteworthy that no case has been found in Australia or Iceland, where the ordinary hydatid is specially common. It has been described in cows, sheep, and pigs; it has been thought that the infection is thus conveyed to man (Posselt).

Nature.—A good deal of discussion has taken place as to the nature of alveolar hydatid disease, *i.e.* whether it is merely an exogenous form of the ordinary echinococcus (Virchow) or an entirely distinct parasite. Klemm⁸ found the ordinary *Taenia echinococcus* in the intestine of a dog fed on the alveolar hydatid, but it is possible that the taenia was present in the dog previously; for Mangold,⁹ and subsequently Müller,¹⁰ by giving the scolices to animals, obtained a taenia different from that of the ordinary echinococcus. The geographical distribution of the two forms does not correspond, as it should do, on the supposition that alveolar hydatid is merely the result of exogenous multiplication of the ordinary echinococcus. Melnikow-Raswedenkow, from exhaustive researches, concludes that the alveolar hydatid is quite distinct from the ordinary echinococcus cyst. According to his views, it should be regarded as belonging to the class of the infective granulomas, and be comparable to tuberculosis, actinomycosis, and syphilis, since it manufactures a special toxin which causes inflammation followed by coagulation-necrosis.

The embryo reaches the liver by the portal vein, becomes embedded

¹ Melnikow-Raswedenkow. *Studien über den Echinococcus alveolaris*, 1901.

² Posselt. *Deutsches Arch. f. klin. Med.*, 1899, lxiii, 457.

³ Dicaulfoy. *Manuel de pathologie interne*, tome ii, p. 773.

⁴ Bruyant. *Bull. hist. et scientif. de l'Auvergne*, 1899.

⁵ Rénou. *Compt. rend. Soc. Biol.*, 1900, lii, 167.

⁶ *A Textbook of Medicine*, by Fagge and Pye-Smith, 1902, ii, 459.

⁷ Osler. *Practic of Medicine*, p. 37, ed. vi, 1905.

⁸ Klemm. *Inaug. Dissert.*, München, 1883.

⁹ Mangold. *Berlin. klin. Wehnschr.*, 1892, xxix, 50.

¹⁰ Müller. *München. med. Wehnschr.*, 1893, xl, 225.

in one of the portal spaces, and develops into a chitinous multilocular mass which corresponds to a proglottis of a taenia and not to a hydatid cyst. The parasite becomes encysted and produces ova which are spherical or oval, and measure from 170 to 1000 μ in diameter; an embryo encysted in the liver may produce 15 to 16 ova. In the production of ova when in the human body this cestode resembles the trematode worms, such as the liver fluke (*Fasciola hepatica*). The embryos, being endowed with amoeboid movement, invade the tissues, set up inflammatory and degenerative changes, and may be destroyed by phagocytosis. When the embryos get into the hepatic veins, they may set up metastases in the lungs, brain, etc.

As already pointed out, alveolar hydatid leads to an exogenous formation of cysts, and thus contrasts with the endogenous production of daughter cysts inside the parent cyst which characterises the ordinary echinococcus in man.

Morbid Anatomy.—The liver is enlarged, but may not be otherwise abnormal externally; it may be nodular from the projection of the parasite, and from perihepatitis be adherent to the diaphragm or to surrounding parts. According to Posselt's statistics, the right lobe is affected alone in 65 per cent of the cases, and the left lobe exclusively in 10 per cent. The posterior part of the right lobe is the seat of election. The tumour is surrounded by a fibrous capsule containing an alveolar arrangement of irregular cavities, some of which are occupied by the gelatinous hydatid cysts, others by caseous, purulent, or bile-stained debris. The appearance is much like that of colloid carcinoma. The contents of degenerated cysts may eventually resemble mortar from admixture with lime salts. The liver is hard from fibrosis, which may involve more distant parts of the organ, and may grate under the knife from calcareous infiltration. Occasionally large cystic spaces may form. The unaffected part of the liver undergoes compensatory hypertrophy. The bile-ducts are often compressed, and inflammation may spread to the vessels in the portal spaces and set up endophlebitis, lymphangitis, and obstruction and obliteration. The naked-eye appearances may suggest colloid carcinoma, or, from the sponge-like structure, actinomycosis.¹ Secondary alveolar hydatids may occur in the lymphatic glands, lungs, peritoneum, kidneys, brain. By direct extension the right adrenal may be infected.

Histology.—The parasite shews a structureless wavy membrane, which is covered both internally and externally by an embryonic parenchymatous layer giving rise to scolices. The alveolar hydatid thus differs fundamentally from the ordinary hydatid which has an internal parenchymatous layer (or endocyst) only (Melnikow-Raswedenkow). The outer parenchymatous produces scolices, living amoeboid embryos, and toxins, and thus sets up extensive inflammation in the surrounding tissues and metastases. The scolices are developed in the outer parenchymatous layer, and are therefore exposed to the action of phagocytes, and as a result are difficult to find. The tumour is alveolar, the fibrous tissue being derived from the

¹ Compare Wynne. *St. Barth. Hosp. Rep.*, 1889, xxv, 159.

liver; the spaces contain colloid material—the chitinous vesicles of the parasite—which, as the result of coagulation-necrosis and caseation, forms a mass like a gumma. By softening a cavity may result, and in the debris calcareous granules, cholesterol, and haematoidin crystals may be seen. The periphery of the tumour shews active proliferation of the connective-tissue cells with the production of fibroblasts, giant cells, and endarteritis obliterans. The liver cells may be fatty.

Clinical Features.—The disease is usually seen in persons between twenty-five and fifty years of age, and occurs more often in men than in women, according to Vierordt, in the proportion of 3 (males) to 2 (females). The onset is very gradual, and usually the first symptoms are referred to the region of the liver, and consist of pain, weight, and discomfort. On examination the liver is enlarged and feels hard and resistant and its edge firm; the surface may be smooth, or nodular when the parasite invades the capsule. In the latter event it will be tender, and pain may be due to perihepatitis. In rare cases fluctuation and softening appear in the hepatic tumour. Dévé refers to 2 cases in which there was a gaseous abscess.¹

The spleen is said to be enlarged in 90 per cent of the cases (Posselt). Jaundice occurs in four-fifths of the cases. It may be the first thing noticed and tends to become deep. As a result cholaemia with multiple haemorrhages may develop. In rare instances the jaundice intermits and varies from time to time. As jaundice may depend on obstruction inside the liver, bile may still pass into the duodenum. Ascites is much less frequent than jaundice; it may be due to pressure on the portal vein, or to chronic or tuberculous peritonitis (Teutschlaender²). Oedema of the legs may occur in the late stages of the disease, and in rare instances depends on pressure on the inferior vena cava. The urine may be of low specific gravity and so copious as to imitate diabetes insipidus. Eosinophilia is inconstant. Some cases shew irregular fever and excessive perspiration; in this connexion it should be remembered that tuberculosis is said to supervene in 3 per cent of the cases (Posselt). Emaciation is a late event, and thus contrasts with the course of events in malignant disease of the liver. Digestive disturbances are not uncommon, such as dyspepsia, nausea, vomiting, diarrhoea, or constipation. In some instances there is thirst or a voracious appetite, and in these cases the bodily weight may increase.

Course and Duration.—The disease is very chronic, and may last for ten or more years. Death may be due to increasing weakness or to cholaemia.

Diagnosis is extremely difficult, and the disease will probably be regarded as malignant until the liver is carefully examined. This mistake has been made even when the liver has been exposed by laparotomy. The slow course of the disease may arouse a suspicion as to its real nature. Removal of a fragment of the growth at a laparotomy and microscopic examination have established the diagnosis, but mere puncture

¹ Dévé. *Rev. de chir.*, Paris, 1907, xxxv, 556.

² Teutschlaender. *Corr.-Bl. f. schweiz. Ärzte*, 1907, xxxvii, 406.

is of no value. It may also be mistaken for hypertrophic biliary cirrhosis or cysts of the pancreas. If the liver is enlarged and no localised tumour is palpable, the presence of jaundice and splenic enlargement may suggest biliary cirrhosis. But the jaundice is much deeper than in biliary cirrhosis, and the enlargement of the spleen comes on later in the course of the disease.

Prognosis.—The difficulty of diagnosis accounts for the fact that most cases are recognised after death, and that, as far as our knowledge goes, the prognosis is bad. But it is to be hoped that comparatively early operation and excision of the growth will give good results.

Treatment consists in excision of the affected part of the liver, and should be undertaken as early as possible. Bruns¹ successfully treated a case by excision of the parasite. Merely tapping has not been found to be successful. Injection of formalin into the tumour has given encouraging results.

FATTY LIVER

UNDER the heading of "fatty liver" it will be convenient to consider together the changes formerly described separately as fatty infiltration and fatty degeneration. It will be well, however, to state briefly what is meant by the two terms. Fatty infiltration or accumulation is an exaggeration of the physiological storage of fat in the hepatic cells; it is normally present in young children, in pregnant and nursing women, sometimes in healthy adults who have died suddenly from accidents, and constantly in obesity. Fatty degeneration, originally regarded as the pathological production of fat at the expense of the protoplasm of the liver cells, may be described as the appearance of fat in injured cells, the fat being an index rather than the direct result of the cell degeneration (Christian²). For a full consideration of the subject of fat metabolism the reader should consult Adami's *Principles of Pathology*, 1911, i, 905. The histological differences between the two conditions are described on page 430, but in practice they are frequently combined. It is better, therefore, to speak of pathological fatty change in the liver.

Etiology.—Pathological fatty change in the liver is met with in a number of conditions which have in common the presence of toxins in the blood. Thus, a fatty state of the liver cells is the most constant change found in the bodies of alcoholic persons, and experiment shews that this must be regarded as due to the effect of alcohol as a protoplasmic poison. Numerous other poisons lead to the same change, *e.g.* phosphorus, arsenic, antimony, copper, chloroform, iodoform, sulphuric, oxalic, carbolic, tartaric, and other acids, sulphonals.³

¹ Bruns. *Beitr. z. klin. Chir.*, 1896, xvii, 201.

² Christian, H. A. *Johns Hopkins Hosp. Bull.*, 1905, xvi, 6.

³ Taylor and Sailer, *Contributions from the William Pepper Laboratory*, Philadelphia, 1900, p. 120; and Garrod, *Lancet*, 1900, ii, 1323.

Rosenfeld¹ has proved experimentally that the fatty change produced in the liver by phosphorus and phloridzin is not due to the local formation of fat from the protoplasm of the hepatic cells but to the transport of fat from other parts of the body; for if the animal is previously starved no accumulation of fat occurs in the liver.

A certain amount of fatty change is induced by numerous bacterial toxins, and may occur in typhoid fever, pneumonia, puerperal fever, cholera, diphtheria, small-pox,² scarlet fever, erysipelas, and streptococcic infections.³ Fatty change in the liver is very frequent in pulmonary tuberculosis. Louis found it in 40 out of 120 fatal cases. It is thought to be more frequent in female than in male patients (Budd⁴). It is very striking to find extensive fatty change in the liver of an emaciated patient with little or no subcutaneous fat. Frerichs⁵ regarded the fatty condition of the liver as due to the absorption of fat from the subcutaneous and other parts of the body and sometimes to imperfect secretion of bile. This explanation will not stand against the facts that in cases of emaciation and jaundice, as, for example, carcinoma of the head of the pancreas compressing the bile-duct, there is often no fatty change in the liver. The administration of fatty food and cod-liver oil can hardly account for the change, inasmuch as cod-liver oil was not used in Louis' time (Wilson Fox⁶). Insufficient oxidation depending on the condition of the blood cannot be an exclusive or essential cause, since fatty change in the liver is much less marked in emphysema, chronic bronchitis, and congenital morbus cordis than in pulmonary tuberculosis. The fatty liver in tuberculosis is at the present time referred to retrogressive or degenerative changes set up by poisons reaching the liver. Whether this is due to the tuberculous toxin alone seems doubtful.

Péron⁷ found that intravenous injections of cultures of virulent tubercle bacilli lead to extensive fatty degeneration of the liver, an effect which was prevented if the cultures had previously been raised to 100° C. for five minutes; but Carrière⁸ as a result of injection of tuberculin produced cloudy swelling, vacuolation, and necrosis of the liver cells, but never any fatty or lardaceous change. The latter experiments suggest that the fatty degeneration is due to the effects of toxins other than those of the tubercle bacillus, such as might result from secondary streptococcic infections.

Fatty change in the liver cells is met with in intestinal diseases, such as dysentery and diarrhoea, and would therefore appear to be due to the action of poisons absorbed from the alimentary canal.

¹ Rosenfeld. *Ztschr. f. klin. Med.*, 1895, xxviii, 256.

² Arnaud. *Marseille méd.*, 1899, p. 39.

³ Roger et Garnier. *Rev. de méd.*, 1901, xxi, 97.

⁴ Budd, G. *Diseases of the Liver*, p. 304, ed. iii, 1857.

⁵ Frerichs. *Diseases of the Liver*, vol. i, pp. 285, 301. Transl. New Sydenham Soc., 1860.

⁶ Wilson Fox. *Treatise on Diseases of the Lungs and Pleuræ*, p. 620, 1891.

⁷ Péron. *Compt. rend. Soc. Biol.*, 1898, 10. s., v, 446.

⁸ Carrière. *Arch. de méd. expér. et d'anat. path.*, Paris, 1897, ix, 65.

Thus, in 32 cases of gastro-enteritis in children Thiemich¹ found fatty change in 23; Freeborn² noted a similar condition in 50 per cent of cases of diarrhoea in children under three years of age. Freeman³ found that out of 496 children dying of various diseases the liver was fatty to the naked eye in 202, or 41 per cent, and that this change was common in acute infectious diseases and in disease of the alimentary tract, but rare in other chronic wasting disorders. Menetrier⁴ described fatty liver due to a grave infection of appendicular origin.

Fatty change is also met with in grave anaemia, and is probably due to the poisons giving rise to the anaemia. It is also well marked in cases fatal from the status epilepticus (Mott⁵), in diabetic coma, in fatal cases of acid intoxication after anaesthesia in children,⁶ and in cyclical vomiting,⁷ all of which are toxic conditions.

Fatty change in the liver is frequent in the bodies of pregnant women, and is very probably due to the diseases or morbid conditions responsible for death. As pointed out in other parts of this work, fatty change is frequently associated with other lesions of the liver, such as cirrhosis, lardaceous disease, and chronic venous engorgement. It is then due to some poison, to impaired nutrition, or to both factors. In some instances acute fatty transformation of the liver cells occurs and proves fatal with much the same clinical manifestations as acute yellow atrophy. In some cases there is no clear evidence as to the nature of the toxic or infective cause. It has been noted after operations, and has been thought to be due to chloroform, iodoform, carbolic acid, or to a combined action of toxins due to disease and of chloroform (*vide* also p. 579).

Stiles and M'Donald⁸ argue that the fatty change in the liver is entirely due to the action of chloroform on a previously healthy liver. Wells⁹ suggests that chloroform kills the cells but leaves their intra-cellular enzymes intact, so that self-digestion or autolysis occurs; he further suggests that the oxidising enzymes are acted upon while the lipase is free to form fat.

Morbid Anatomy.—When the liver cells rapidly undergo fatty change the organ is much enlarged, for example, in phosphorus poisoning, and in extreme cases a weight of even 10 pounds has been reached.

In 1890 a woman aged sixty-seven, who for years had been a heavy drinker and lately had consumed a bottle of whisky a day, was admitted into St. George's Hospital deeply jaundiced, unconscious, and with scarcely audible

¹ Thiemich. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1896, xx, 179.

² Freeborn. *Acad. Med. New York*, Jan. 1897.

³ Freeman. *Arch. Pediat.*, 1900, xvii, 81.

⁴ Menetrier. *Bull. et mêm. Soc. méd. des hôp. de Paris*, 1903, 3. s., xx, 1115.

⁵ Mott. *Arch. Neurol. Claybury*, 1899, i, 491.

⁶ Compare cases and remarks by L. G. Guthrie, *Lancet*, 1894, i, 193, 257; and 1903, ii, 10; *Clin. Journ.*, 1907, xxx, 129; Brackett, Stone, and Low, *Boston Med. and Surg. Journ.*, 1904, cli, 2; Bevan and Favill, *Journ. Amer. Med. Assoc.*, 1905, xlv, 754.

⁷ Langmead. *Practitioner*, 1912, lxxxix, 29.

⁸ Stiles and M'Donald. *Rep. Soc. Study Dis. Child.*, Lond., 1904, iv, 208.

⁹ Wells. *Journ. Am. Med. Assoc.*, 1906, xlvi, 341.

heart sounds ; the urine did not contain leucine or tyrosine. At the necropsy which I performed, the liver weighed $10\frac{3}{4}$ pounds and floated in water ; microscopically, besides very extensive fatty change, there was some apparent increase in the amount of the fibrous tissue. The heart, 16 ounces, shewed fatty degeneration. The process was probably acute, though less so than in acute yellow atrophy. Such cases might perhaps be called acute yellow hypertrophy.

The enlargement affects all parts equally and the normal shape of the liver is retained, the edges becoming rounded and thicker. When the fatty change comes on slowly, enlargement is much less marked and some fatty livers are of a normal size or occasionally small. A fatty liver is usually uniformly smooth on the surface, and as seen after death, anaemic. The consistency varies, being sometimes firm, and this without any fibrosis ; sometimes soft and friable.

In a boy aged three years who died as the result of poisoning from the absorption of iodoform from a wound the liver weighed 30 ounces and was remarkably firm, keeping its shape and impressions like His' model. Microscopically there was marked fatty change but no fibrosis or lardaceous disease. During life high temperature, delirium, and wasting were present.

These differences in the consistency of a fatty liver may depend on conditions preceding death, such as infective agencies leading to acute changes, or may be the result of post-mortem decomposition. On section the lobules are often very distinctly mapped out so that the surface has a granular appearance exactly like that of unilobular cirrhosis. It is often impossible to be certain as to the existence of cirrhosis or not until microscopic sections have been made. In other cases in which the fatty change affects the cells of the lobules universally the cut section is uniform and has no resemblance to cirrhosis. The specific gravity of the liver is diminished and the organ may float in water. When cut into, the surface of the section may be soft and yielding, or in some instances firm. The dry blade of a knife is rendered greasy by the exuding oil when the organ is soft. If put into a flame, the fat melts, may burn in a spluttering manner, and if allowed to drop on paper, leaves an oily stain. The fat may amount to 25 to 30 per cent of the weight of the liver. There may be local haemorrhages and focal bile-staining due to extravasation, depending on degeneration and rupture of these vessels. Local areas of fatty change are not uncommon in the liver in infective cases ; they are due to the local action of the toxins produced on the spot by micro-organisms in the vessels of the liver.

Histologically the liver cells contain globules of fat of varying sizes which are refractive and stain black with osmic acid, red with Sudan III and Scharlaeh R, and various colours with basic aniline dyes by Lorrain Smith's¹ method. The fat is found most often in the central zone, least often in the median zone of the lobule (M'Crae and Klotz²).

A distinction has been drawn between fatty degeneration and fatty

¹ Lorrain Smith. *Brit. Med. Journ.*, 1906, ii, 149.

² M'Crae and Klotz. *Journ. Exper. Med.*, N.Y., 1910, xii, 746.

infiltration of the liver cells. Thus, in fatty infiltration the cells chiefly at the periphery of the hepatic lobules are occupied by globules of fat of considerable size, whereas in fatty degeneration the fat occurs in small

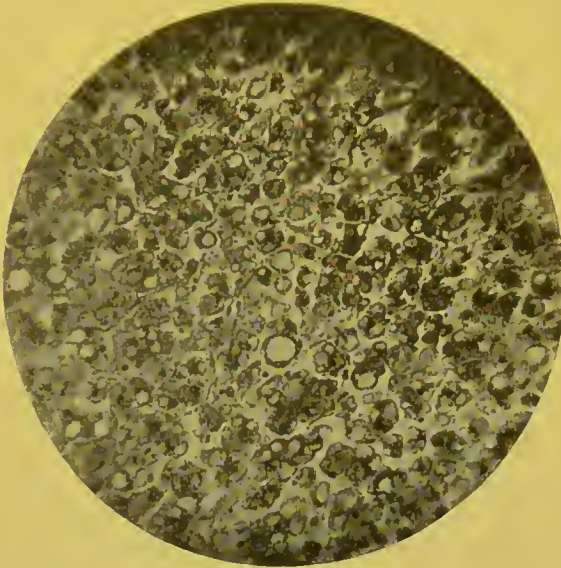


FIG. 54.—Extensive fatty change in the liver cells, the result of acute toxic changes. (Photomicrograph by Dr. S. G. Penny.)

granules which, according to M'Crae and Klotz, do not run together to form globules. These granules are most frequent in the central zone. In fatty infiltration the protoplasm of the liver cells is mechanically displaced to the side of the cell by the deposited fat. In fatty degeneration the cells are degenerated, their cytoplasm granular, and the nucleus shews chromatolysis, but is in its ordinary position. After removal of the fat in cases of infiltration the cells return to their normal state, whereas in degeneration they break up. Well-marked examples

of the two processes are quite distinct, but they are frequently combined and it is often impossible to draw a rigid line between them.

A review of the pathology of fatty degeneration and infiltration shews that there is no proof that fat arises directly from degeneration of the protein molecule of the liver cell. The factors which lead to so-called "fatty degeneration" lower the vitality of the cells and thus favour deposit of fat (lipins), which, owing to injury, the cell cannot utilise. Instead of "fatty degeneration" the term "degenerative fatty infiltration" should be employed (Herxheimer and Walker Hall¹).

The fibrous tissue of the portal spaces shews up so as to suggest some old fibrosis, and frequently there is some small-celled infiltration in and around the portal spaces; this is due to wasting and atrophy of the essential liver parenchyma, and may be called a "replacement fibrosis." Though in miniature much the same as hepatic cirrhosis, it is unimportant, and should be regarded as dependent on the fatty change and should not be spoken of as fatty cirrhosis, but as fatty liver. In this way any confusion between this condition and genuine cirrhosis with superadded fatty change is avoided.

Clinical Picture.—*Signs.*—In cases of general obesity the liver may be made out by percussion to be enlarged, but it may be difficult to feel the

¹ Herxheimer and Walker Hall. *Med. Chronicle*, Manchester, 1904, xl, 227.

edge distinctly, both because the abdominal walls are overloaded with fat and because during life the enlarged fatty liver is often soft. Fatty liver is indeed very often latent and unsuspected. The skin may be greasy, the arterial pressure is usually low, and the heart sounds distant or feeble. Fat women often have remarkably small chests, and in the dead-house the contrast between the enormous fatty covering and the size of the thoracic cavity is most striking.

In cases in which a fatty liver is associated with definite disease, such as pulmonary tuberculosis, the liver is enlarged and smooth, but is less firm than in lardaceous disease or cirrhosis, and therefore not so easily

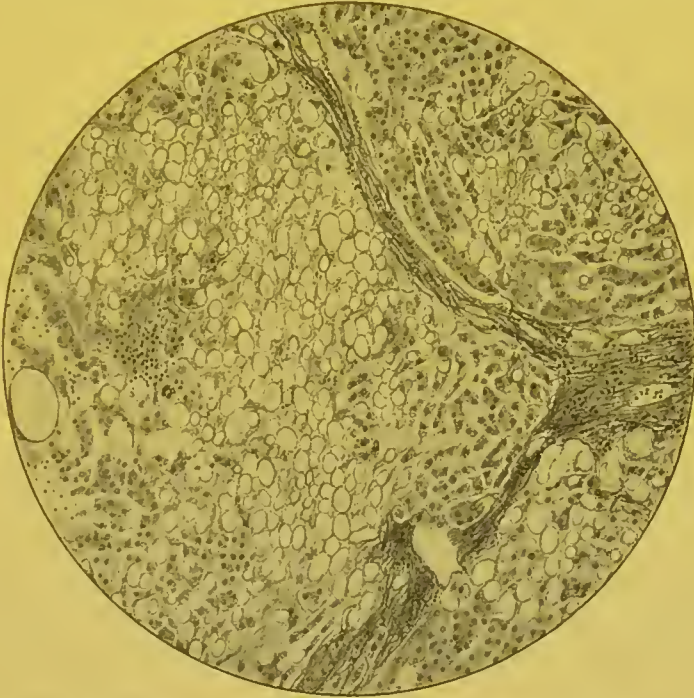


FIG. 55.—Microscopical appearances of extensive fatty change in the liver cells. Some groups of cells are free from change, while in others hardly any protoplasm is left. There is an apparent increase of the interlobular fibrous tissue, suggesting slight multilobular cirrhosis. $\times 72$.

felt. The spleen is not enlarged. The stools are light. Jaundice does not occur in uncomplicated cases; and there is no portal obstruction, so that there is no ascites or enlargement of the subcutaneous abdominal veins. Piles have been said to occur, but this is probably a coincidence. Addison¹ laid stress on the condition of the skin accompanying fatty liver—bloodless, looking like fine polished ivory, almost semi-transparent, and exquisitely smooth, like satin. This change was earliest seen and best marked on the backs of the hands. Addison also referred to recurring attacks of oedema in cases of fatty liver, especially in alcoholic patients. Possibly the oedema was due to peripheral neuritis or cardiac dilatation. It has been suggested that an enlarged fatty liver may inter-

¹ Addison, T. *Guy's Hosp. Rep.*, 1836, i, 476.

ferre with the action of the diaphragm, and so cause massive collapse of the lower lobe of the right lung (Goodall and Kingsbury¹).

The ammonia in the urine may be increased at the expense of the urea. This should be regarded not as evidence of failure in the urea-forming power of the liver cells, but as evidence that the morbid process underlying the fatty change, for example, phosphorus poisoning, leads to the formation of organic acids which fix the ammonia and prevent its conversion into urea.

Lépine and Eymonnet² described excess of glycerophosphoric acid in the urine; this is derived from lecithin, which they found to be present in excess in fatty livers. Haematoporphyrinuria is often seen,³ and may be due to failure of the fatty liver to arrest the urobilin which reaches it from the alimentary canal.

The **symptoms** are those of the condition or disease responsible for the secondary change in the liver. No doubt the various functions of the liver are not so well performed as in health, but there is no constant or pre-eminent failure of function. When the degeneration is very acute and extensive, the symptoms approach those of acute atrophy, although actually the liver is much larger than normal. But the condition then ceases to be one of ordinary fatty liver.

The diarrhoea formerly thought to depend on fatty liver is probably the cause rather than the effect. There is no pain associated with fatty liver.

As a result of severe trauma fat from the liver might pass into the hepatic veins and give rise to fat embolism of the lungs (Engel⁴).

In *delayed chloroform poisoning* the cases fall into two groups: (a) with fatty change in the periphery of the lobules, mainly in children, presenting the signs of acid intoxication, and hardly ever jaundice; (b) mainly in young adults with jaundice and the symptoms and gross morbid appearances of acute yellow atrophy (chloroform necrosis of the liver; H. G. Wells⁵).

Diagnosis.—Painless enlargement of the liver, with a smooth, comparatively soft surface, in an individual in whom one of the known causes of a fatty liver, such as alcoholism or pulmonary tuberculosis, is active, should suggest its presence. It must be diagnosed by exclusion of the following conditions:

(1) Leukaemic infiltration of the liver leads to a firmer condition and can be at once recognised by examination of the blood.

(2) ~~Cardiac disease~~. The liver is much firmer than in fatty liver, and there may be signs of ~~cardiac~~ disease of the kidneys (albuminuria), splenic enlargement, or diarrhoea.

(3) ~~Cirrhosis, especially an enlarged cirrhotic liver with latency of the~~

¹ Goodall and Kingsbury. *Brit. Med. Journ.*, 1911, ii, 815.

² Lépine et Eymonnet. *Lyon méd.*, 1882, xli, 15.

³ Garrod. *Lancet*, 1900, ii, 1323.

⁴ Engel, H. *München. med. Wchnschr.*, 1901, xlviii, 1046.

⁵ Wells, H. G. *Arch. Int. Med.*, Chicago, 1908, i, 594.

Amyloidosis /
amyloid

symptoms. In the absence of symptoms the diagnosis is very difficult, and turns chiefly on the surface of the liver; if it is smooth, fatty change is probable; if irregular, cirrhosis is indicated. In numerous instances fatty change is associated with cirrhosis.

(4) A displaced liver if movable is at once recognised, but if displaced by some undetected cause, such as a pleural effusion or pneumothorax, it might be regarded as a large fatty liver.

(5) Enlargement due to a deep-seated hydatid cyst or abscess. Here the liver is much more prominent and more easily felt and mapped out, while there may be signs of pressure, pain, or fever.

Prognosis.—Patients with fatty livers, being often chronic alcoholics, are bad subjects for operation and bear severe illness—such as pneumonia, and erysipelas, and accidents—very badly. Symonds,¹ Verneuil,² and L. Guthrie³ insisted on the danger of operations on these patients; and Guthrie, who has pointed out that chloroform narcosis is specially dangerous in patients with fatty livers, has recorded a series of cases in children in which symptoms suggesting acid intoxication followed operations, and in which a fatty liver was found after death. Gilbert and Lereboullet⁴ have drawn attention to the frequency with which pneumonia proves fatal in cases in which the liver is fatty, and insist that death results in such cases, not from hepatic disease, but because of it. Apart from the dangers attending operations and acute illness the prognosis of fatty liver is that of the accompanying disease or condition.

The treatment of fatty liver is that of the primary cause, such as obesity or pulmonary tuberculosis. In cases in which symptoms of acid intoxication come on after chloroform or ether narcosis, large doses of bicarbonate of sodium should be given by the mouth, rectum, or intramuscular transfusion; glucose 6 per cent solution may also be given by the mouth or rectum (Beddard⁵).

Amyloid

LARDACEOUS DISEASE

Lardaceous

Synonym: Amyloid, Waxy, Chondroid (Wells) Disease of the Liver.

HOPE figures an undoubted case of lardaceous disease in his work on "Morbidity Anatomy" (1834) as "hypertrophy of the red substance of the liver." In 1857 Budd⁶ described it as "scrofulous disease of the liver."

Incidence and Etiology.—The liver is not so often affected as the

¹ Symonds. *Med. Times and Gaz.*, 1860, ii, 351.

² Verneuil. *Gaz. méd. de Paris*, 1892, 8. s., i, 447.

³ Guthrie, L. *Lancet*, 1903, i, 10; 1905, ii, 583. *Clin. Journ.*, 1907, xxx, 129.

⁴ Gilbert et Lereboullet. *Bull. et mém. Soc. méd. des hôp.*, 1902, 3. s., xix, 577.

⁵ Beddard. *Lancet*, Lond., 1908, i, 782.

⁶ Budd, G. *Diseases of the Liver*, p. 312, ed. iii, 1857.

spleen and kidneys. In the combined statistics of Birch-Hirschfeld, Loomis, Dickinson, Goodhart, and Turner, there are 795 cases of lardaceous disease, in which the spleen was affected in 585, the kidney in 539, and the liver in 387.

The causes of lardaceous change in the liver are those of lardaceous disease generally, namely, prolonged suppuration and syphilis without necessarily any associated suppuration; and grave cachectic conditions due to chronic and severe toxæmias occasionally appear to be responsible for it. Tuberculosis *per se* does not give rise to the lardaceous change, but when a tuberculous lesion becomes secondarily infected lardaceous disease may develop. This is seen in chronic pulmonary tuberculosis, hip-joint disease, or caries of the spine with psoas abscess.

Incidence in chronic pulmonary tuberculosis: in 326 cases tabulated by West¹ lardaceous disease was met with in 20, or 6·2 per cent; in Wilson Fox's series of 91 cases the percentage was as high as 15.

The lardaceous change is usually produced slowly after months of suppuration, but it has been found in the liver one month after the onset of osteomyelitis (Soyka). This acute lardaceous change has also been produced in animals (Krawkow,² A. B. Green³).

Prolonged suppuration is now so comparatively infrequent that lardaceous disease is less common, and relatively more often due to syphilis than formerly. As a result of congenital syphilis, lardaceous change is seen as a late result, but it hardly ever occurs in association with the intercellular cirrhosis. In delayed hereditary syphilis it may be combined with gummas or with parasymphilitic multilobular cirrhosis (*vide* p. 379). The lardaceous change may be local in the liver around a gumma, an abscess, or a suppurating hydatid. This points to the conclusion that the change is due to a toxin derived from the abscess or gumma. Lardaceous disease is occasionally seen in other infective conditions, such as chronic malaria. Brault and Legry⁴ suggest that grave intestinal lesions, such as tuberculous ulceration, are specially prone to produce lardaceous change in the liver.

Lardaceous change may be associated with lymphadenoma in the liver without any other cause,⁵ and I have seen it in chronic lymphatic leukaemia. Early lardaceous change has been described in four cases of fatal rheumatic fever (Beattie⁶). A

Pathogeny.—The lardaceous substance is a glycoprotein containing chondroitin-sulphuric acid, and is apparently due to the action of a poison or poisons on protoplasm. A Krawkow⁷ considered that infection was absolutely necessary,

¹ West. *Diseases of the Respiratory Organs*, 1902, ii, 426.

² Krawkow. *Arch. de méd. expér. et d'anat. path.*, Paris, 1896, viii, 106.

³ Green. *Journ. Path. and Bact.*, Edin. and Lond., 1901, vii, 184.

⁴ Brault et Legry, in *Manuel d'histologie pathologique*, Paris, 1912, iv, 829.

⁵ Buchanan, *Glasgow Med. Journ.*, 1889, ii, 117; Fagge and Pye-Smith's *Textbook of Medicine*, ii, 647, ed. iv.

⁶ Beattie. *Brit. Med. Journ.*, 1906, ii, 1444.

⁷ Krawkow. *Centralbl. f. allg. Path. u. path. Anat.*, 1897, xl, 195.

^ It may occur in pure actinomycosis (Dean), in rheumatoid arthritis of children (Herringham)
Cases certainly occur with any ^{generally recognized} ~~satisfactory~~ cause; I know of two cases associated with chronic intestinal stasis

^ It is not uncommon in horses which have been injected with diphtheria toxin for the
production of antitoxic serum (LEWIS)

DEAN. Brit. med. Journ., 1912, ii, 1303.

Herringham. Kidney Diseases, p. 350, Oxford, 1912.

LEWIS. Journ. Med. Research, 1906, xv, 449.

The left lobe may
show a loss
for the spleen

and that the lardaceous change did not follow aseptic suppuration such as that set up by turpentine. He regarded the change as due to the absorption of microbial poisons, and, like Czerny, looked upon lardaceous disease as an infiltration rather than a local degeneration.

Morbid Anatomy.—The liver is enlarged and may weigh more than twice its normal amount; it has been known to weigh 14 pounds (Wilks¹). The surface is smooth, usually anaemic, and may shew a few stellate veins. The enlargement is uniform, and the shape of the organ is so well preserved that the impressions of adjacent viscera recall His' anatomical model. The margins of the liver are firm and rounded. It is extremely firm and can be cut into thinner slices than a healthy organ. It has a rubbery feel, but is not so resistant to the knife as a cirrhotic liver. Its specific gravity is increased, and has been found to be 1080 (Wilks) instead of the normal 1055. The liver is anaemic, but its colour varies with the degree of anaemia; it may resemble the fat of bacon or, when less anaemic, smoked salmon. The lobular arrangement is accentuated. The connective tissues of the walls of the gall-bladder and ducts are said to shew the change in a high proportion of the cases of widespread lardaceous disease, 11 out of 12 cases (Zabczynska²). The glands in the portal fissure may be considerably enlarged, but do not press on the bile-ducts or portal vein. As in other organs, the lardaceous change, when slight, may not be manifest to the naked eye, and microscopic examination or staining with iodine may be necessary.

Iodine Stain.—The existence of lardaceous disease of the liver should be tested for in the post-mortem room by the iodine reaction. A solution of iodine in water, containing a little iodide of potassium to dissolve it, the dilute liquor iodi of the Pharmacopoeia U.S.A., or Lugol's solution (iodine 1 part, iodide of potassium 2 parts, water 200 parts), should be used. The tincture of iodine should not be employed, since the spirit it contains partially coagulates albumin, and thus obscures the reaction. The cut section should first be washed to remove any blood, and since alkali interferes with the reaction, should be treated with dilute acetic acid. The solution of iodine should then be poured upon it, or, better, a thin slice of the liver should be placed in a beaker of the watery solution of iodine. The selective action of iodine is then well shewn; the healthy parts are coloured yellow, while the lardaceous parts become of a dark mahogany. The intermediate zone of the lobules stands up as a brown ring on a yellow ground. The colour changes on the addition of H_2SO_4 , but does not actually turn blue, as was originally described, but becomes a dark violet or allied tint.

Microscopic Examination.—The chief brunt of the disease falls on the capillaries in the intermediate zone of the lobules, which appear swollen, homogeneous, and tortuous. They compress and to a great extent conceal the hepatic cells, while the narrowing of the lumen of the capillaries impedes the flow of blood through them, and as a result the liver cells

¹ Wilks, S. *Lectures on Pathological Anatomy*, p. 455, 3rd ed., 1889.

² Zabczynska. *Rev. méd. de la Suisse Rom.*, 1911, xxxi, 815.

atrophy and degenerate. On section the swollen homogeneous curves of the capillaries imitate the appearance that would be presented by swollen hepatic cells, but the latter can be made out in appropriately stained specimens between the enlarged capillaries, and never become lardaceous. The lardaceous change in the capillaries eventually spreads throughout the lobule, and may then invade the intralobular vein. The fibrous tissue of the portal space remains healthy, and cirrhosis does not occur as the result of the cellular changes.

Although the capillaries are the part of the hepatic vascular system chiefly attacked by the lardaceous change, examination of livers in which the change is commencing may shew that the first part to be affected is the middle coat of the small arteries, as is seen around a gumma, the muscular coat being irregularly attacked; eventually, if the change is excessive, it may attack the walls of the portal and hepatic veins. The lardaceous material lies between the muscular fibres of the media and not in them; it spreads inwards to the intima, but does not involve the endothelium, which may shew fatty change.

Microscopic sections may be examined fresh, with iodine solution, or preferably with methyl-aniline violet.

Staining Reactions.—With methyl-aniline violet in watery solution the lardaceous capillaries are stained red, ~~while~~ ^{and} the healthy tissues are coloured violet; this stain is better shewn if the sections are washed in water acidulated with acetic or hydrochloric acid. It is a much more delicate stain than the iodine one, and it seems probable that it reacts to an earlier stage of lardaceous change than iodine. When the lardaceous change is very far advanced, the methyl-aniline violet reaction may fail, while the iodine reaction continues to be marked. Other substances, such as colloid or hyaline, occasionally stain like lardaceous tissue. Krawkow considers that the reaction is more easily obtained in fresh sections, and that slight degrees of it may not be shewn if the tissues are previously hardened. Gentian violet ~~may also be employed; it~~ has the same selective staining effect. [^]

Clinical Picture.—*Symptoms.*—Lardaceous disease of the liver is usually subordinate either to the primary condition to which it is due or to the general manifestations of widespread lardaceous disease, for it is rare for the liver to be the only organ affected. There are no symptoms pathognomonic of lardaceous disease affecting the liver to the exclusion of the other viscera. Jaundice does not occur unless there is some other factor, such as a gumma. Ascites if present is in all probability due to concomitant cirrhosis, gumma, chronic peritonitis, or renal disease.

A boy under my care with a lardaceous liver due to psoas abscess had oedema of the legs, great development of the caval veins over the abdomen, and ascites. The ~~was obliterated~~ ^{ED} of the inferior vena cava. The ascites was due to extension of inflammation from the spine to the peritoneum and mesentery which was thickened. Tirard¹ recorded a somewhat similar case.

¹ Tirard, N. *Medical Treatment*, Lond., 1900, p. 338.

^ Hadley described as Achromo-amyloid a liver which has the naked-eye and microscopic appearances of lardaceous change, but ~~path. soc.~~ did not give any of the staining reactions; and Davidson subsequently described this condition as an early stage of ~~the~~ amyloidosis.

Hadley. Trans. Path. Soc., Lond., 1899, 4, 134.

DAVIDSON.

Ascites does, however, occasionally occur in uncomplicated instances of lardaceous liver. It may be part of general oedema, or terminal and due to extreme cachexia. Bolton¹ records 3 cases of extreme ascites in children, and points out that it is commoner in children than in adults. It is remarkable that although the liver is almost universally lardaceous, there is little clinical evidence of functional inadequacy. It has, it is true, been thought that the bile is diminished in amount, and that the faeces become pale. The liver is free from pain or tenderness unless there is some complication, such as abscess, perihepatitis, growth, or gumma.

Signs.—The only real evidence of lardaceous disease of the liver is its enlargement, which is uniform, smooth, and painless. It is only when combined with gumma, cirrhosis, perihepatitis, or in the rare event of a secondary growth in a previously lardaceous liver that the surface becomes rough and nodular. The left lobe of the liver may be so prominent as to suggest primary malignant disease (Musser²), or an enlarged spleen (Affleck³). Clubbing of the fingers with osteo-arthritis has been observed in lardaceous disease of the liver secondary to spinal caries (Symes-Thompson⁴).

Diagnosis.—Under this heading the other forms of painless enlargement of the liver must be mentioned. In every case it is important to determine if the causes for lardaceous disease are or have been present, and if there are any signs of renal or intestinal disease of the same nature.

In the absence of anaemia and some degree of wasting the probabilities are against hepatic enlargement being lardaceous. In leukaemia the liver is enlarged, but a blood examination will settle any doubt. When lymphadenoma attacks the liver, there will almost certainly be enlarged glands elsewhere and fever. Simple fatty liver is less readily felt and, as a rule, is associated with obesity. In pulmonary tuberculosis an enlarged liver may be due to fatty change or to lardaceous disease, and to settle the question the other signs of lardaceous disease must be looked for; if all of them, such as albuminuria, dropsy, diarrhoea, enlarged spleen, are absent, it may be assumed that the liver is fatty.

A hydatid cyst deep in the substance of the organ may so displace the liver forwards as to imitate the physical signs of a lardaceous liver, but the other symptoms and causes of lardaceous disease are wanting, and the patient's general health is usually so good as to put lardaceous disease out of court. A large cirrhotic liver may, from its size and firmness, imitate a lardaceous liver. In both diseases the spleen may be enlarged, and when ascites occurs in lardaceous disease the condition may easily be regarded as cirrhosis. Evidence of past suppuration, albuminuria, and of past syphilis, are in favour of lardaceous disease; a history of alcoholism and haematemesis point to cirrhosis. The following

¹ Bolton. *Clin. Journ.*, Lond., 1907, xxxi, 117.

² Musser, J. H. *Proc. Path. Soc.*, Phila., 1898-9, n. s., ii, 202.

³ Affleck, J. O. *Trans. Edin. Med.-Chir. Soc.*, 1898, xvii, 61.

⁴ Symes-Thompson. *Med.-Chir. Trans.*, Lond., 1904, lxxxvii, 130.

case illustrates the difficulties which may arise in correctly diagnosing between these two conditions:—

A woman aged forty-seven was under my care in St. George's Hospital in June-July 1900 with ascites, oedema of the legs, albuminuria, and signs of pulmonary tuberculosis at both apices. There was a history of haematemesis, and the facial aspect was that of cirrhosis. She was tapped twice, and then passed into a drowsy condition from which she rallied temporarily after transfusion. At the autopsy there was lardaceous disease of the liver (53 ounces) and kidneys due to chronic pulmonary tuberculosis. Microscopically there was no fibrosis of the liver. There was slight thickening of the capsule of the liver and opacity of the peritoneum. It is possible that the lardaceous condition of the liver, together with the slight peritoneal change, was responsible for the ascites. It is probable that what was described as haematemesis was in reality haemoptysis.

Prognosis.—When the liver is enlarged so that it is readily felt, and there is reason, from the history, to believe that it is due to lardaceous disease, the prognosis is bad, since the disease is likely to attack the kidneys and the intestines. The affection of the liver itself does not make so much difference, but it is evidence that the disease is present and may affect more important organs.

Under ~~appropriate~~ treatment a lardaceous liver may diminish in size. In Duckworth's¹ recorded a case in which it diminished by half before death occurred, and previously Graves² described great improvement in cases which were probably of the same nature. ~~Experimentally~~ Lubarsch³ ~~has shown that lardaceous disease may pass away; he excised a piece of a lardaceous spleen from an animal some weeks before death, and after death no evidence of lardaceous change was present.~~

Treatment.—The first step is to remove the cause if it is still present. Suppuration should if possible be submitted to surgical treatment so as to bring it to a rapid and satisfactory termination. When syphilis is the cause, iodide of potassium should be given, while good results have also been obtained from iodide of iron. If there be concomitant renal disease, the effect of iodide must be carefully watched, as an iodide eruption is then more readily produced. I have seen such an eruption closely resemble a uraemic rash. The general health requires careful attention; and sea air, good food and hygienic surroundings, bitter tonics, iron, and acids do good. Alkalis have been recommended, chiefly on theoretical grounds, but do not succeed better than, if so well as, acids. Budd and Warburton Begbie recommended chloride of ammonium, but its utility is very doubtful. Constipation may require attention, but mild laxatives should be given, otherwise severe diarrhoea may be set up. Diarrhoea may be very troublesome, and by exhausting the patient lead to a fatal issue; it may alternate with constipation, and should be treated by

¹ Duckworth. *St. Barth. Hosp. Rep.*, 1874, x, 57.

² Graves. *Clinical Medicine*, i, 518, New Sydenham Soc., 1884.

³ Lubarsch. *Virchows Arch.*, 1897, cl, 471.

(Herringham)

Herringham. Kidney Diseases, p. 353, Oxford, 1912.

according to Mallory, Parker, and
Nye the liver cells contain
haemofuscin or haemosiderin
in 3 per cent. of all necropsies
excluding Cuntz's (vide p.)

astringents, and if necessary with opium. General dropsy requires cardiac tonics, iron, and diuretics; the skin should be made to act freely by diaphoretics and hot baths, or the amount of fluid should be restricted.

PIGMENTATION

THE subject of pigmentation in association with cirrhosis is described under the head of Pigmented Cirrhosis (p. 302). It is merely necessary here to mention the various conditions in which the liver cells contain pigment. The pigments may be divided into: (I) Intrinsic, or those produced in the body and derived from the blood or bile; and (II) extraneous pigments introduced into the body; these are of comparatively little importance.

I. Intrinsic pigments are those derived from the blood, namely, *haemosiderin*, which contains iron, *haematoidin*, an iron-free body, and the bile pigment.

~~*Haemosiderin*~~^{3,13}.—The cells of the liver may contain *haemosiderin*—~~an iron-containing pigment derived from the destruction of red blood-corpuscles and the haemoglobin thus liberated~~—in a number of conditions. In a systematic examination of the liver in 300 cases, Castaigne¹ found that in 31, or more than 10 per cent, the liver cells contained *haemosiderin*; ~~In portal cirrhosis haemosiderin is not uncommon in the liver cells (Abbott,² Kretz).~~ The reaction (Perl's test) for *haemosiderin* consists in placing microscopic sections in a 2 per cent solution of ferrocyanide of potassium for three minutes, transferring to a 1 per cent solution of hydrochloric acid for two to five minutes, and washing in distilled water; the pigment granules take a bluish-green colour, which is well seen in the cells in the periphery of the lobule in pernicious anaemia. It also occurs in leukaemia, in some cases of enteric fever, and chronic intestinal disorders. Contact with iron lifters must be avoided in performing this test. Adami³ considers that *haemosiderin* is deposited around the diplococcic form of the colon bacillus, described by him, in the liver cells. ~~Bacterial haemolysis has been thought to account for haemosiderosis of the liver cells in ordinary cirrhosis (vide p. 207) and in haemochromatosis (vide p. 303). In haemochromatosis the liver cells also contain haemofuscin.~~ *Haemosiderosis* of the liver is also seen after haemorrhage into the peritoneal cavity, in fatal purpura, and has been produced by experimental haemolysis; for example, by toluylenediamine (Meunier⁴). In some cases of new growth in the liver the hepatic cells in the neighbourhood of the growth shew *haemosiderin*. I have also seen it in lymphadenoma. In malaria the liver cells may contain

¹ Castaigne. Quoted by Chauffard, *Traité de Médecine* (Bouchard-Brissaud), v. 240, ed. ii, 1902.

² Abbott, M. *Journ. Path. and Bacteriol.*, Edin. and Lond., 1901, vii, 55.

³ Adami. *Journ. Amer. Med. Assoc.*, 1899, xxxiii, 1506.

⁴ Meunier. *Thèse de Paris*, 1897-8, No. 171.

haemosiderin, and it has also been described in association with suppuration. According to Biondi,¹ Kupffer's star-shaped cells take up haemosiderin.

Haematoidin.—This iron-free pigment is seen in and between the liver cells around the intralobular vein in chronic venous engorgement of the liver (*vide* p. 90.) It may also occur in the neighbourhood of haemorrhages, angiomas, scars of old abscesses, gummas, etc.

In the various forms of biliary obstruction the liver cells are degenerated and occupied by granules of *bile pigment*.

II. **Extrinsic Pigmentation**.—In *Anthraxis*, *Silicosis*, etc.—In rather rare instances particles of carbon or of other foreign substances have been found in otherwise normal livers; the liver of cirrhosis (*vide* p. 302) may shew impregnation with particles of carbon—cirrhosis anthracotica (Welch²); [Lancereaux³ described this condition in copper-workers]; of stone (Adami⁴), and of silver after its medicinal use for epilepsy (Frommann⁵). Reference has been made elsewhere (p. 302) to a case of cirrhosis in a sweep with pigmentation, probably due to soot, of the fibrous tissue. These conditions are interesting curiosities, but have no clinical significance.

CALCIFICATION

THIS condition, which is a pathological curiosity, occurs in two forms—primary and secondary.

Primary calcification is very rare; it may occur in the liver cells, in the connective tissue, or in the walls of the vessels. In three cases this calcification was associated with chronic nephritis.

In a boy aged sixteen years who died with scarlatinal dropsy, Bristowe⁶ found infiltration of the liver cells with an earthy salt which dissolved in acetic acid. In a boy aged seventeen years who died from chronic pulmonary tuberculosis and parenchymatous nephritis, Mihel⁷ found that the liver, which grated under the knife and had the aspect of chronic venous engorgement, shewed calcareous infiltration of the liver cells around the intralobular veins. The infiltration appeared to be due to calcium phosphate. In a girl aged fourteen years who died with advanced interstitial nephritis the liver was found by Brill and Libman⁸ to shew calcification with calcium phosphate around the branches of the hepatic artery, which was affected with endarteritis obliterans. The liver shewed chronic perihepatitis and chronic venous engorgement.

Babes⁹ refers to a case, fatal from tuberculous disease of the hip, in

¹ Biondi. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1895, xviii, 174.

² Welch. *Johns Hopkins Hosp. Bull.*, 1891, iii, 32.

³ Lancereaux. *Traité des maladies du foie et du pancréas*, p. 380, 1899.

⁴ Adami. *Sajous' Annual*, 1898, ii, 313.

⁵ Frommann. *Virchows Arch.*, 1859, xvii, 135.

⁶ Bristowe, J. S. *Trans. Path. Soc.*, 1857, viii, 233.

⁷ Mihel. Quoted *Phila. Med. Journ.*, 1901, vii, 199.

⁸ Brill and Libman. *Journ. Exper. Med.*, N.Y., 1899, iv, 541.

⁹ Babes. *Virchows Arch.*, 1886, cv, 511.

which the liver shewed areas of calcification, regarded as due to the deposit of salts absorbed from the affected bones. Sprunt¹ described calcification of the elastic tissue in the liver and spleen in a case of infective biliary cirrhosis due to a stone in the common duct. In a case of widespread calcification of the arteries and endarteritis associated with hydronephrosis in a child aged six months the hepatic artery was similarly affected, but the liver was microscopically healthy (Hale White and Bryant²). Though calcification of arteries in the liver is extremely uncommon in man, it is said not to be rare in horses.

In secondary calcification a deposit of calcareous salts occurs in inflammatory products of considerable age, such as gummas, the scars of cured abscesses, the walls of hydatid cysts, and in the walls of the gall-bladder as the result of past or chronic inflammation. A remarkable example of diffuse calcareous infiltration of the liver recorded by Targett³ was probably secondary to syphilitic inflammation (*vide* Fig. 44).

Carrel⁴ recorded a psorospermial tumour of the liver which underwent calcification. The tumour was removed in a laparotomy undertaken with the view that it was a calcified gall-bladder. Chemically the salts chiefly present were carbonate and phosphate of calcium.

Sometimes hard, coral-like masses, of about the size of a marble, are found embedded in the liver. They are probably the dried-up remains of biliary cysts or, in other words, intrahepatic calculi. Small bile cysts without any general biliary obstruction are occasionally seen; as time goes on their contents become more viscid and eventually solid. Small calcified masses with a fibrous capsule which represent the larvae of *Linguatula rhinaria* are not very rare in the liver (Kaufmann⁵).

LEUKAEMIC INFILTRATION

Synonym: Leucocythaemic Infiltration.

THE liver may be greatly enlarged in leukaemia, especially in the lymphocytic form; not uncommonly it weighs 5 or 6 pounds instead of 2½, and may weigh much more; a weight of 13 pounds has been noted.

Murchison⁶ described a case which, from the illustration given of the blood, was evidently myeloid leukaemia, with a liver that was smaller than natural, weighing 35 ounces. In the two following cases of myeloid leukaemia examined after death at St. George's Hospital the liver was much enlarged. The liver of

¹ Sprunt. *Journ. Exper. Med.*, N.Y., 1911, xiv, 59.

² Hale White and Bryant. *Guy's Hosp. Rep.*, 1901, lv, 17.

³ Targett. *Trans. Path. Soc.*, Lond., 1889, xl, 123.

⁴ Carrel. *Lyon méd.*, 1900, xciii, 89.

⁵ Kaufmann. *Lehrbuch der spez. Path.*, 1907, S, 594.

⁶ Murchison. *Diseases of the Liver*, p. 308, ed. ii, 1877.

a man aged twenty-six weighed $7\frac{1}{2}$ pounds, and the spleen 6 pounds; scattered through both these organs were white spots resembling miliary tubercles, but due to dense infiltration with leucocytes. The liver of a woman aged twenty-seven weighed 10 pounds and the spleen 76 ounces. Together these two viscera occupied almost the whole of the front of the abdomen, a few coils of intestine only appearing above the pubes. There was no ascites. The enlargement of the liver was, contrary to what is usually seen, almost entirely of the right lobe and not of both lobes.

imitating **Morbid Anatomy.**—The surface of the liver is pale and smooth. On section it is pale and may shew accumulations of leucocytes either in the larger portal spaces or in the substance of the liver. In rare instances there are pinkish white masses around the portal spaces; less rarely there are white spots ~~exactly like miliary tubercles in the liver substance.~~ Microscopically these are areas of dense leucocytic infiltration and not tuberculous granulation tissue. In the condition described as chloroma, which forms a connecting link between leukaemia and tumours, the portal canals have been found to be marked out as green tracks.

In a case of acute myeloid leukaemia there were tumour-like masses due to blood in the liver and spleen (Miller¹).

Microscopically, the appearances are not always exactly alike. There may be a general and diffuse crowding of the capillaries with leucocytes with some increase at the periphery of the lobules; or there may be intense leucocytic infiltration around the portal spaces at the periphery of the lobules, with comparatively little blocking of the intralobular capillaries. When there is marked infiltration at the margin of the lobules the lobulation is clearly seen with the naked eye, and the microscopic appearances at first sight suggest interlobular inflammation, e.g. suppurative pylephlebitis. The leucocytes are chiefly large or small mononuclears; in myeloid leukaemia myelocytes are seen in the capillaries. The liver cells, especially in the centres of the lobules, may stain imperfectly, from degeneration depending on impaired nutrition, and may be fatty or atrophied. At the periphery of the lobule the hepatic cells are sometimes pigmented with haemosiderin and resemble the appearances in pernicious anaemia. On chemical analysis the amount of iron has been found to be increased. Milne² has observed extensive hyperplasia of the liver cells in lymphocytic leukaemia. Cirrhosis does not develop as the result of leukaemic infiltration, but Mosse³ reported a case of lymphocytic leukaemia cured by x-rays, in which fatal cirrhosis followed and was thought to be due to damage done to the liver cells as a result of destruction of large numbers of leucocytes.

Clinical Features.—There is really nothing which can be specially correlated with leukaemic infiltration of the liver in a case of leukaemia

¹ Miller. *Journ. Path. and Bacteriol.*, Cambridge, 1912, xvi, 143.

² Milne. *Ibid.*, 1909, xiii, 131.

³ Mosse. *Berlin. klin. Wchnschr.*, 1908, xlv, 1219.

/ but due to massing of white cells.

1/ and ascites.

In myeloid leukaemia the capillaries are crowded with cells similar to those in the spleen and bone marrow, and the liver cells may atrophy from pressure so that capillary telangiectases may give rise to small whitish areas visible to the unaided eye. There is little infiltration outside the capillaries.

In lympho^{id} ~~leukaemia~~ leukaemia there may ^{be} extensive intra-acinar infiltration of the liver lobules

The hepatic enlargement may increase after the spleen has diminished in size under ^{h.c.} x-rays, probably from the presence of leucocytic waste products in the liver (Tixier and Troisier).

Tixier et Troisier. Gaz. des hôp. de Paris, 1910

except the painless enlargement of the liver. [^] Jaundice does not occur ; in the latter stages of leukaemia ascites is not uncommon ; it has been suggested that this may be due to pressure of leucocytic infiltration on the intrahepatic branches of the portal vein, or to pressure of enlarged glands in the portal fissure on the portal vein. But it seems more probable that it is due to some concomitant chronic peritonitis and to the cardiac debility and altered blood-state. It is conceivable that ascites might be in some degree determined by thrombosis in the terminal branches of the portal vein in the liver. The urine in a case of leukaemic

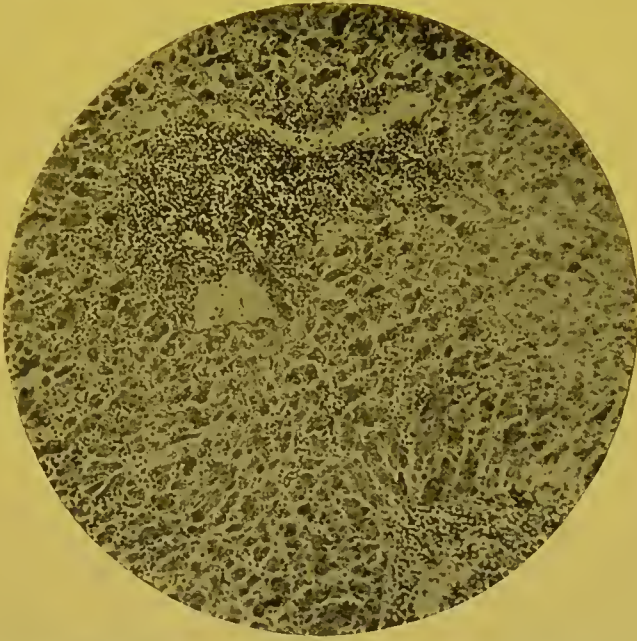


FIG. 56.--Liver in leukaemic infiltration. There is dense leucocytic massing around a vein and an excessive number of white blood-corpuscles in the capillaries. The liver cells stain badly. (Photomicrograph by Dr. S. G. Penny.)

infiltration of the liver was found to contain haematoporphyrin by Garrod,¹ who was inclined to regard this pigment as specially related to the hepatic change. The urine shews excess of uric acid.

The diagnosis of leukaemic infiltration of the liver depends on an examination of the blood. This should be done in a doubtful case of hepatic and splenic enlargement in order to prevent the disease being regarded as lardaceous or syphilitic and treated with iodide of potassium. In very acute leukaemia the liver may be tender as well as enlarged, and the fever and the severe constitutional condition may, if no glands are palpably enlarged, closely imitate hepatic abscess (Emerson²).

The prognosis and treatment are, of course, those of leukaemia.

¹ Garrod, A. E. *Lancet*, 1900, ii, 1323.

² Emerson. *Johns Hopkins Hosp. Bull.*, 1907, xviii, 80.

CYSTS

THE various forms of cysts which occur in the liver may be conveniently classified as follows:—

1. *Parasitic Cysts*.—Echinococcic or hydatid cysts (*vide* p. 391.)

2. *Cysts manifestly due to Biliary Obstruction*.—There may be widespread dilatation of the bile-ducts in the liver in long-standing biliary obstruction. The ducts stand out under the capsule and contain mucous fluid. This change is entirely secondary to the cause of the obstructive jaundice, such as carcinoma of the head of the pancreas, and will not be further discussed here. The effects of biliary obstruction may be more localised and give rise to definite cysts, which in exceptional instances may be of very considerable size; in North's¹ case a cyst containing five pints of coffee-coloured fluid was associated with a calculus impacted in the common bile-duct.

In a man aged thirty-nine who died in St. George's Hospital with jaundice supervening in the course of pancreatic diabetes complicated with rapid pulmonary tuberculosis, there were remarkably large intrahepatic calculi composed of bilirubin.² There were biliary cysts on the surface of the liver, with inflamed walls and fibrosis spreading outwards into the surrounding liver substance (*vide* Fig. 105). Merle³ described cystic dilatation in a liver extensively tuberculous, presumably due to obstruction of the ducts.

3. A few words may be said about *cysts occurring in cirrhosis* of the liver. They are very rare and may arise in two distinct ways: (a) By biliary retention, and then resemble those just described; (b) by the softening down of the adenomatous masses seen in nodular cirrhosis. (a) These cysts are small, sometimes microscopic, and are only of pathological interest. The following is an example of macroscopic cysts:—

A woman aged forty-four years died with ascites and cirrhosis in St. George's Hospital. The liver, 41 ounces, was finely granular and shewed microscopically multilobular cirrhosis, passing in parts into unilobular cirrhosis. On the convexity of the right lobe near the falciform ligament there was a cyst the size of a hazel-nut with clear contents, and near it a dried-up cyst with thick walls and almost calcareous contents. The liver (Fig. 6) also shewed the effects of tight lacing.

Microscopic cysts or dilatations of the small bile-ducts are occasionally seen.

In making microscopic sections of a hobnailed liver weighing 41 ounces, I found dilatation of the bile-ducts in the portal spaces. This case shewed perihepatitis, chronic peritonitis, and small calculi in the gall-bladder, but there was no history or evidence of past biliary obstruction. (*See also* Fig. 34.)

¹ North. *Med. Rec.*, N.Y., 1882, xxii, 344.

² Rolleston. *Trans. Path. Soc.*, Lond., 1898, xlix, 133.

³ Merle. *Arch. de méd. expér. et d'anat. path.*, Paris, 1909, xxi, 353.

Costantini and Dubouche
consider that these cysts are
~~due to~~ cystic dysembryomas
and due to the same
process as is polycystic
disease

Costantini et Dubouche Journ. de Chir., Par., 1923, xxi, 1

(b) The adenomatous formations seen in nodular cirrhosis may soften down and form false cysts resembling those seen in degenerating new-growths; cysts due to degenerative changes in carcinoma and sarcoma of the liver are described on page 491.

4. *Simple Cysts*.—They are usually single or present in very small numbers; when there are a large number, the condition becomes that of cystic disease (*vide* p. 447). As a rule, the cysts are small and of no clinical importance. Larger simple cysts are sometimes met with. Probably some of those recorded are sterile hydatid cysts; microscopic examination of the cyst wall should decide the point. Cysts sufficiently large to contain many pints have been described.

In Bayer's¹ and Winckler's² cases there were 13½ pints, in Aldous',³ 12 pints, and in North's, 5 pints of fluid.

Mode of Formation.—Simple cysts ~~are usually~~ ^{have been} regarded as due to retention from local obstruction of the bile-ducts, and Bland-Sutton⁴ suggests ~~that the pressure exerted by the corset may lead to obstruction and dilatation of a bile-duct.~~ Although in a fully developed stage they do not contain bile, they may do so in an early stage.

has been suggested
as a cause
(Bland-Sutton)

Thus, in a woman aged thirty-five years who died in St. George's Hospital in 1892, with peripheral neuritis and pulmonary tuberculosis, there was a small cyst containing bile in the left lobe of the liver.

The bile disappears from the cyst probably in the same way that it does in general biliary obstruction of long standing, and becomes replaced by clear albuminous fluid. It has been thought that a bile-containing cyst may be due to rupture of an intrahepatic bile-duct (Doran⁵). Other methods of origin have been suggested for simple cysts of the liver, such as dilatation of the glands of the larger bile-ducts or dilatation of aberrant bile-ducts (Mosehcowitz, *vide* p. 454); the last view would explain the cysts as due to a congenital malformation. Again, some of the small single cysts with blood-stained contents may, as in the spleen, be the result of degenerative changes in angiomas. A large single cyst may be due to cystic change in an adenoma of the bile-duct, the papillomatous growth softening down in the same way as an adenoma of the thyroid.

Shattuck⁶ reports such a cyst containing a gallon of clear fluid (*vide* p. 458).

Morbid Anatomy.—The cysts are commoner on the surface of the liver than in its substance, but they are seldom pedunculated; Doran refers to three large pedunculated cysts. A cyst, the size of a child's head, in the round ligament of the liver, described by Henderson,⁷ was

¹ Bayer, K. *Prag. med. Wchnschr.*, 1892, xvii, 637.

² Winckler. Quoted by Doran.

³ Aldous. *Brit. Med. Journ.*, 1911, ii, 688.

⁴ Bland-Sutton, J. *Ibid.*, 1905, ii, 1167.

⁵ Doran, A. *Med.-Chir. Trans.*, 1904, lxxxvii, 1.

⁶ Shattuck. *Boston Med. and Surg. Journ.*, 1900, cxlii, 427.

⁷ Henderson. *Ann. Surg.*, Lond., 1909, i, 550.

probably of a different nature from cysts in the liver. They are usually surrounded by a firm fibrous capsule which often contains numerous blood-vessels, and in cases of old standing may shew calcareous infiltration. The walls of recent cysts are thin. The inner surface is smooth, but is often ridged, possibly from the remains of partitions between originally separate cysts, and may resemble the inside of the auricles of the heart. It has an opaque white colour, except in very thin-walled cysts.

A typical specimen occurred in the liver of a man aged sixty-three who died of a thoracic aneurysm; on the surface of the convexity of the liver, near the falciform ligament, there was a cyst the size of a hazel-nut, with traces of partitions but not completely multilocular. In a man aged seventy-eight years, who had granular kidneys with a few minute cysts, the liver, which otherwise appeared natural, contained four cysts; three of them were on the surface of the liver, the other was deeply embedded in the substance of the right lobe; it was the largest, and measured $\frac{3}{4}$ of an inch across. The contained fluid was straw-coloured and the walls were smooth.

The larger simple cysts must be distinguished from hydatid cysts by examination for hooklets and for laminated membrane, and during an operation the relations of the cyst must be noted in order to differentiate it from idiopathic dilatation of the extra-hepatic bile-ducts. The contents of these cysts vary considerably. They are usually clear and colourless, but may be bile- or blood-stained, green, reddish, or brown. From degenerative changes in the lining epithelium the contents may become syrupy, as in some renal cysts, and so dry up and form solid white encapsulated masses of small size. The fluid is albuminous and may contain blood or epithelial cells, haematoidin, bile pigment, cholesterin, tyrosine.¹ In Doran's case the cyst contained $2\frac{1}{2}$ pints of bile. It is probable that as the result of injury extravasation of blood or of bile may take place into a cyst with clear serous contents.

Microscopic Appearances.—The capsule is composed of laminated fibrous tissue which may contain bile-ducts, sometimes dilated, and occasionally blood pigment. The fibrous tissue invades the liver tissue for a very short distance, and is lined internally by a layer of epithelial cells which may be columnar, cubical, or polyhedral in the small cysts. In exceptional instances, of which Zahn² has collected 14 examples, the epithelium may be ciliated. In the larger cysts the cells are absent or much flattened.

Clinical Features.—Simple serous cysts are rarely large enough to give rise to signs or symptoms. When they do, the signs are usually like those of hydatid cysts, or occasionally of an ovarian cyst, and the treatment is the same. Rupture into the peritoneal cavity may occur, and when large, induce shock and collapse. In rare instances severe haemorrhage may occur into a large cyst and even prove fatal.

¹ Campbell M'Donnell. *Lancet*, 1900, i, 453.

² Zahn. *Virchows Arch.*, 1896, cxliii, 175.

Jaundice has been noted in
some cases (DORAN, MUNK)

MUNK Berlin Klin. Wchnschr. 1912, XLIX, 2174
Woman 44

Jones collected 61 cases
operated upon

MUNK. Berlin. Klin. Wchnschr., 1912, XLIX, 2174
Shaw and ELTING. Arch. Pediat., N.Y., 1909, XXVI, 916
Boyd, S. Lancet, Lond., 1913, i, 951.
Jones, J.F.X. Ann. Surg., 1923, LXXIII, 68.

Kilvington¹ mentions a case which died with symptoms like those of rupture of a large internal aneurysm, from haemorrhage into a large simple cyst of the liver.

¹ ~~Doran's~~² patient was markedly jaundiced.

Usually simple serous cysts are found accidentally at the autopsy, and more often in middle-aged persons. Durante³ ~~met~~^{met} with ~~them~~^{them} in ~~infants~~^{infants} in whom there was no evidence of general cystic disease of the liver. Sharp⁴ recorded a cyst containing three quarts of fluid in a boy aged seven years.²⁴ Large cysts are more often seen in females than in males; in ~~18~~²⁸ cases ~~1~~⁴ were females and ~~1~~⁴ males (Sidney Boyd).

and Shaw
and others
ELTING

Diagnosis.—When of such a size as to be palpable, they can only be distinguished from hydatid cysts by examination of the fluid (*vide* p. 405).

The *treatment* is excision of as much of the cyst wall as is possible; this can be carried out most successfully when the cyst is pedunculated. When embedded in the liver the cyst should be dealt with on the same lines as hydatid cysts.

Cyst of the Round Ligament.—A cyst the size of a child's head was removed from a man aged forty-one by Henderson.⁵

CYSTIC DISEASE

THE liver may be occupied by numerous cysts of varying sizes, and thus presents a contrast to the single or isolated cysts already referred to. This condition is spoken of as cystic disease of the liver.

Incidence.—From their age-incidence the cases may be divided into two categories—those seen in adult life and those found in the newly born—though it is probable that those seen in adult life are also congenital, but, being less marked, have survived.

Comparatively few cases have been reported in *newly born infants*; but the disease is doubtless often overlooked, as it may not be manifest until the liver is examined microscopically. I have seen two cases, in both of which the naked-eye appearances were rather those of fibrosis than of cystic disease. As some cases of cystic livers in infants have been associated with deformities, such as polydactylism, it is probable that if the livers of monsters and stillborn children were systematically examined microscopically, congenital cystic disease of the liver would be found to be less rare.

¹ Kilvington. *Intercolon. Med. Journ. Australasia*, 1902, vii, 557.

² Doran, A. *Med.-Chir. Trans.*, 1904, lxxxvii, 1.

³ Durante. *Bull. Soc. Nat.*, Paris, 1902, lxxvii, 953.

⁴ Sharp. *South African Med. Rec.*, 1906, iv, 39.

⁵ Henderson. *Ann. Surg.*, 1909, 1, 550.

Cases have been reported by Kanthack and myself,¹ Still (2),² Bar and Rénon,³ Couvelaire,⁴ Couvelaire and Porak,⁵ Carré,⁶ Brindeau and Macé,⁷ Kilvington,⁸ Bunting (2),⁹ Sikes,¹⁰ Mcader.¹¹ In all these cases the kidneys were also markedly cystic. Borst¹² recorded a case in a child seven months old, Dudgeon¹³ a case which was probably of this nature in a child of nine months in which the kidneys were normal; W. Müller¹⁴ a case in a female child two years of age whose abdomen began to swell at ten months, and Batty Shaw¹⁵ a case in a child aged three and a half years. These cases support the view that the less marked congenital cases may persist into adult life.

Possibly the case of a full-term child the subject of many abnormalities, including cystic kidneys, obliteration of the bile-duct, and communicating cysts, one in each lobe of the liver, belongs to this group; no microscopic examination, however, was made (Witzel¹⁶). Gueniot's¹⁷ case may also belong to this category. A full-term fetus had 6 fingers and 6 toes, anencephaly, absence of external genitals, kidneys three times the normal size, and a cyst in each lobe of the liver; the cyst in the left lobe contained 40 grams and that in the right lobe 80 grams of clear fluid. This was the eighth child of a woman who married her nephew; none of the children, some of whom shewed abnormalities, survived.

Association with Cystic Disease of the Kidneys.—Real cystic disease of the liver is nearly always accompanied by a similar, and almost always more advanced, change in the kidneys. This association was first noted by Bristowe.¹⁸ A few accidental cysts may occur in the liver without any similar change in the kidney, but this hardly constitutes cystic disease. In 85 cases the liver alone was affected in 10 (Moschcowitz¹⁹). Cystic kidneys not uncommonly occur without cystic disease of the liver.

In 63 cases of cystic kidneys collected by Lejars²⁰ 46, or 73 per cent, were free from cystic change in the liver. In 90 cases of congenital cystic disease of the kidneys Luzzatto²¹ found 5 only in which the liver was similarly affected.

¹ Kanthack and Rolleston. *Virchows Arch.*, 1892, cxxx, 488.

² Still. *Trans. Path. Soc.*, 1898, xlix, 155.

³ Bar et Rénon. *Compt. rend. Soc. Biol.*, 1894, xlii, 835.

⁴ Couvelaire. *Ann. de gyn. et d'obstét.*, 1899, lii, 453.

⁵ Couvelaire et Porak. *Compt. rend. Soc. d'obstét. et de gyn. et de pédiat.*, Paris, 1901, p. 26.

⁶ Carré. *Thèse de Paris*, 1901, No. 232.

⁷ Brindeau et Macé. *Gaz. hebdom. de méd.*, Paris, 1899, xlv.

⁸ Kilvington. *Intercolon. Med. Journ. Australasia*, 1902, vii, 557.

⁹ Bunting. *Journ. Exper. Med.*, N.Y., 1906, viii, 271.

¹⁰ Sikes. *Brit. Journ. Child. Dis.*, 1906, iii, 304.

¹¹ Meader. *Johns Hopkins Hosp. Bull.*, 1907, xviii, 354.

¹² Borst. *Festschrift der phys.-med. Gesells.*, Würzburg, 1899.

¹³ Dudgeon, L. *Trans. Path. Soc.*, 1903, liv, 296.

¹⁴ Müller, W. *Virchows Arch.*, 1901, clxiv, 270.

¹⁵ Shaw, H. B. *Lancet*, 1903, i, 1447.

¹⁶ Witzel. *Centralbl. f. Gynäk.*, 1880, 561.

¹⁷ Gueniot. *Bull. Acad. de Méd.*, Paris, 1891, xxv, 169.

¹⁸ Bristowe, J. S. *Trans. Path. Soc.*, 1856, vii, 229.

¹⁹ Moschcowitz. *Am. Journ. Med. Sc.*, Phila., 1906, cxxxi, 674.

²⁰ Lejars. *Thèse de Paris*, 1888.

²¹ Luzzatto. Quoted by Boinet et Raybaud, *Rev. de méd.*, Paris, 1903, xxiii, 8.

Royce. *Am. Journ. Child. Dis.*, 1913, xv, 196.
Leopold and Kunzler, *ibid.*, 1915, x, 367.

In ^{two} ~~the~~ recorded cases of Cystic Kidneys the lungs showed early
Cystic change although this does not appear in the title of
the articles (Royster; Leopold and Kunster).

Still¹ collected 35 cases of combined cystic change in the liver and kidneys, 3 being infants.

Concomitant cysts in other organs, such as the pancreas (Bunting (2), M'Crae²) and spleen (Blackburn, Peacock and Scott³) have been described in a few cases. I have seen the association of ovarian cysts and hydrosalpinges with cystic disease of the kidneys and liver, and of cystic disease of the liver and kidneys in a woman with acromegaly whose pituitary was represented by a large cyst.

Age.—Multilocular cystic disease is usually observed comparatively late in life, apart from the rare cases seen in infants. In 26 cases collected by Still, 17 were over fifty, and 4 over seventy, years of age; the youngest adult case was thirty-nine.

Sex.—Females are more often affected than males—according to Still, in the proportion of 3 to 1, 21 of his 28 cases being females.

Inheritance.—As in cystic kidneys, the disease may be hereditary and occur in several members of the same generation (Rolleston and Kanthack, Kilvington, Bunting).

Morbid Anatomy.—In congenital cystic disease in *infants* the liver is in a majority of the recorded cases little if at all enlarged, and may not present any naked-eye evidence of cystic change, or only a few minute cysts on the surface. In Porak and Couvelaire's case the liver was so large that it impeded delivery and had to be tapped before the fetus, which was greatly deformed, could be extracted. On section the portal spaces are prominent from fibrosis; a few cystic dilatations may appear, but most of them are microscopic. The naked-eye appearances are usually more suggestive of fibrosis than of cystic change. The larger bile-ducts and the gall-bladder are healthy. The contents of the cysts are clear and do not contain bile (*vide* p. 450).

In *adult* cases of cystic disease the liver may be very greatly enlarged, though this is not constant.

MacDonald⁴ records a cystic liver weighing 14 pounds. A cystic liver in the Royal College of Surgeons Museum weighed 13 pounds 7 ounces, and in Roberts'⁵ case the liver weighed 11½ pounds.

A cystic liver from an adult woman may shew the deformity of tight lacing (*vide* St. Bartholomew's Hosp. Museum, No. 2204 D).

The degree of cystic transformation is nearly always much less in the liver than it is in the kidneys. The kidneys are usually megalo-cystic, while the cystic liver is smaller in proportion. The cysts are, however, bigger than those seen in babies, probably from the union of several cysts originally separate. Their size varies very considerably; there may be many small ones, with one or more larger ones. When

¹ Still, G. F. *Trans. Path. Soc.*, 1898, xlix, 155.

² M'Crae, J. *System of Medicine* (Osler and M'Crae), 1909, vi, ~~35~~ 786

³ Peacock and Scott. *Trans. Roy. Acad. Med. Ireland*, Dublin, 1909, xxvii, 317.

⁴ MacDonald. *New York State Journ. Med.*, 1908, viii, 185

⁵ Roberts. *Ann. Surg.*, 1894, xix, 251.

the liver is considerably enlarged there may be several as big as a walnut. In exceptional instances a very large cyst may be formed. In Cleaver's¹ case there were many small cysts and a single large one measuring $7\frac{1}{2}$ inches in circumference.

The cysts appear on the surface of the organ and may thus give rise to considerable deformity. They are surrounded by a capsule of well-formed fibrous tissue. On section the liver is more or less honeycombed by independent cavities. The cysts usually contain clear albuminous fluid, which is sometimes brown, probably from haemorrhage, and may become colloid and inspissated like the contents of some cysts in megalocystic kidneys. They contain proteins, urea, chlorides, and sometimes blood and epithelial cells, cholesterin, oxalate of calcium, leucine, and creatinine,² but not bile. There is a considerable increase in the amount of fibrous tissue in the liver. The large bile-ducts and the gall-bladder are free from any special change. The association of tuberculosis of the liver with cystic disease has been described (Merle³)

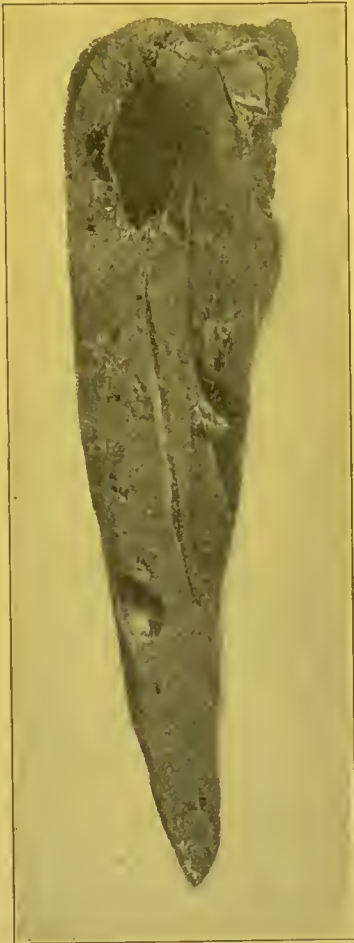


FIG. 57.—Section of cystic disease of the liver in an adult. (Photographed by Dr. H. Morley Fletcher.)

Microscopical Appearances.—In the cystic livers of *newly born infants* there are a number of tubules in the portal spaces which are lined with subcolumnar epithelium and are somewhat dilated. They closely resemble dilated bile-ducts, but are far more prominent and appear to be more numerous than the normal bile-ducts. In sections they may completely encircle the interlobular vein. From the portal space these dilated tubes can be traced into the interlobular tissue, and are accompanied by fairly well-formed fibrous tissue. These epithelial extensions between the lobules are at first somewhat dilated, but as they pass further away from the portal space they tend to

become solid cylinders, and when cut obliquely, may appear to have more than one layer of lining cells. There are never any masses of bile in these tubes or cysts.

The fibrosis thus tends to be unilobular, with exaggerations around the larger portal canals; there is no intercellular cirrhosis and no evidence of

¹ Cleaver. *Phila. Med. Journ.*, 1901, viii, 1139.

² Forbes, J. G. *St. Barth. Hosp. Rep.*, 1897, xxxiii, 207.

³ Merle, P. *Arch. de méd. expér. et d'anat. path.*, Paris, 1909, xxi, 353.

congenital syphilis. In places blood is extravasated into the substance of the hepatic lobules. The liver cells are usually well preserved; exceptionally they shew vacuolation which is not due to fat, but may be explained as sections of dilated biliary capillaries which, having invaginated or indented the liver cells, give the impression of being inside the cells.

In the *adult form* the cysts are much larger, arise in the portal spaces, and are surrounded by well-formed fibrous tissue, while there may be numerous blood-vessels in the immediate neighbourhood. There is considerable fibrosis of the liver; Blackburn¹ described fibrous nodules due to the conversion of cysts into connective tissue. In the smaller cysts the epithelium is columnar, in the medium-sized cysts it becomes cubical or polyhedral, and in the larger ones it is degenerated, absent, or represented by a few flattened cells. In exceptional cases ciliated epithelium has been described in the cysts.² The bile-ducts in the liver are often dilated in parts, but this is not constant. The hepatic cells are, generally speaking, healthy, but have been found to shew the vacuolated appearance described in congenital cases.

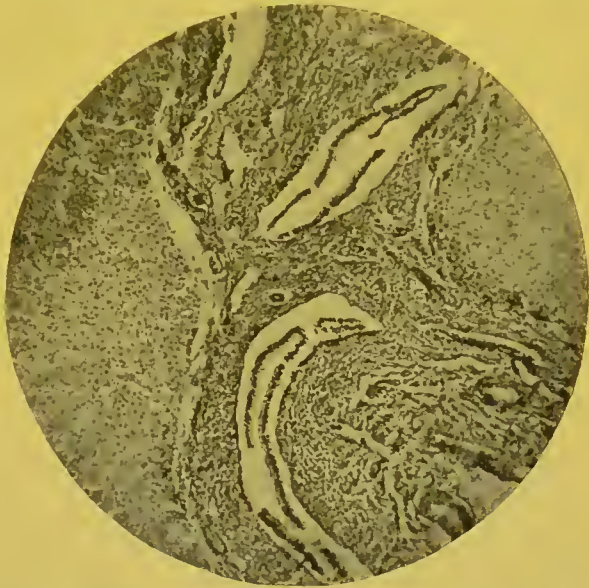


FIG. 58.—Photomicrograph of congenital cystic disease of the liver. Shews portal space with increased quantity of well-formed fibrous tissue and with dilated tubes lined by columnar epithelium, which has separated from the walls in the process of hardening. The hepatic cells shew vacuolation. (By Dr. Harold Spitta.)

Pye-Smith³ regarded this change as due to intracellular cyst formation and to be a degenerative process beginning long after adult life.

A point of interest is the connexion between congenital cystic disease and the similar anatomical condition more often met with in adults. They are so similar that it appears reasonable to regard the adult cases as congenital in origin, and to explain the survival by supposing that the change in the liver and kidneys is less extensive than in the rare cases fatal in infancy. Still regards cystic disease of the liver as a malforma-

¹ Blackburn, C. R. *Trans. Path. Soc.*, Lond., 1904, lv, 203.

² Lejars, *Thèse de Paris*, 1888, p. 34; Hanot et Gilbert, *Maladies du foie*, p. 295, 1888.

³ Pye-Smith. *Trans. Path. Soc.*, 1881, xxxii, 112.

tion which is not progressive, and on this hypothesis it is obvious that, if the subject can survive the early effects, life may be prolonged for years.

The **pathogeny** of eystic disease of the liver has given rise to much discussion. It is so generally combined with a similar change in the kidneys that it is highly probable that the causal factor is the same in both. The following hypotheses bear on the causation of eystic disease of the liver.

Inflammatory Hypothesis.—The oldest view was that there was primary inflammation of the fibrous tissue surrounding the bile-duets, which thus led to dilatation of the bile-duets (Mihalkowicz,¹ Juhel-Renoy, Babinsky, Blackburn). The process might be described as one of pericholangitic inflammation leading to a biliary cirrhosis of the liver with dilatation of the bile-duets. It might perhaps be possible to explain the process as a fairly acute cholangitic and pericholangitic inflammation during fetal life, which so weakens the walls of the small ducts that they then dilate and never recover their proper size, while the inflammatory products organise into firm fibrous tissue. Further, the inflammation might be followed by epithelial proliferation and the formation of new bile-duets.

This explanation of the change in the liver is surrounded with difficulties. If it be regarded as biliary cirrhosis with subsequent dilatation, a form of "epithelial cirrhosis" analogous to cystic disease of the breast, the objection at once arises that in biliary and indeed in the other forms of cirrhosis dilatation of the ducts is extremely rare. A further objection is the absence of jaundice in eystic disease of the liver both in infants and in adults, whereas in congenital obliteration of the bile-duets in which there is an intrauterine inflammation of the intrahepatic bile-duets, practically identical with that postulated by this hypothesis, there is persistent jaundice. The absence of jaundice is rather surprising, whatever view is held as to the origin of the cysts, for if they are not obstructed ducts themselves but independent formations, the real ducts should be pressed upon. This, however, can hardly occur, for there is no bile-staining of the liver or accumulations of inspissated bile in microscopic sections of the liver. It is noteworthy that in the rare condition of chronic pericholangitis (*vide* p. 682), in which the bile-duets must be compressed, there is no trace of jaundice either locally in the liver or elsewhere; it is possible that in both instances this anomaly depends on the lymphatics being obstructed so that bile cannot be absorbed.

Beale² injected the larger bile-duets in Bristowe's case with Prussian blue and found that no injection passed into the cysts; from this he concluded that the formation of cysts did not depend upon closure of a part of the tube and the subsequent accumulation of secretion beyond this point. It is difficult to follow this argument, for if the cysts were due to retention, the injection would not be able to pass the obstruction and flow into the cysts. That injection does

¹ Mihalkowicz. *Thèse de Paris*, 1876.

² Beale, L. *Trans. Path. Soc.*, 1856, vii. 234.

CASTELLI has received this
view. | ^

CASTELLI. Arch. de méd. expér. et d'anat. p.
Paris, 1913, XXV, 623

not pass into the cysts does not, however, prove that the cysts are unconnected with the bile-ducts, for Barratt,¹ in experiments on normal livers, found that when the common bile-duct was injected, under pressures of from 45 to 300 mm. of mercury (the normal pressure under which bile is secreted being 10 to 20 mm. of mercury), with gelatin, none of the injection passed into the bile canaliculi.

Degenerative Hypothesis.—Pye-Smith,² described vacuolation of the liver cells, which by fusion with those formed by other cells led to the formation of cysts. This appearance may be seen in congenital cystic disease of the liver. The vacuoles are probably sections of dilated bile capillaries invaginating the liver cells. Pilliet³ regards cystic disease as a result of atrophy of the liver, the liver cells becoming changed into newly formed bile-ducts and vasa aberrantia, which ~~dilate into multiple~~ *become* cysts.

Hypothesis that the Cysts are a Tumour.—Rindfleisch⁴ believed the cystic change to be a cystic sarcoma starting from the bile-ducts. A number of authors have regarded the changes in the ducts as of an adenomatous nature (Siegmund,⁵ Nauwerk and Hufschmidt,⁶ Workman,⁷ v. Kahlden⁸). Malassez⁹ and Claude¹⁰ considered that the disease was cystic fibro-adenoma homologous with an ovarian cystadenoma. Claude regarded the cysts as dilated new bile-ducts and believed that the process had a special relation to arteriosclerosis. Sabourin¹¹ describes cystic disease of the liver as a cavernous biliary angioma, and regards it as due to irritation which leads to development of new bile-ducts from various sources, such as pre-existing bile canaliculi, possibly from their mucous glands or from vasa aberrantia. The ducts thus formed unite, anastomose, dilate, and lead to the formation of larger ones by the destruction and absorption of the intervening septa. *Λ*

Developmental Hypothesis.—Still put forward an explanation on the same lines as Shattock's¹² view of the nature of cystic kidneys. According to the latter view, the mesonephros persists and its dilated tubules form the cysts, while the metanephros or real kidney is blended with and compressed by the fetal persistence. In the case of the liver, Still¹³ supposes that some of the columns of hypoblastic cells forming part of the duodenal diverticulum develop irregularly and form the cystic tubes, while the bile-ducts proper develop in the ordinary way and can be seen in the portal spaces. The excess of fibrous tissue he regards as a

¹ Barratt, W. *Journ. Path. and Bact.*, 1898, v, 345.

² Pye-Smith. *Trans. Path. Soc.*, Lond., 1881, xxxii, 112.

³ Pilliet. *Tribune méd.*, 1893.

⁴ Rindfleisch. *Lehrb. d. path. Gewebeleh.*, S. 403.

⁵ Siegmund. *Virchows Arch.*, 1889, cxv, 155 (1 plate).

⁶ Nauwerk und Hufschmidt. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1893, xii, 1.

⁷ Workman. *Glasgow Hosp. Rep.*, 1900, ii, 363.

⁸ v. Kahlden. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1893, xiii, 291.

⁹ Malassez. *Progrès méd.*, April 5, 1876.

¹⁰ Claude. *Bull. Soc. Anat.*, Paris, 1896, lxxi, 117.

¹¹ Sabourin. *Arch. de physiol. norm. et path.*, Par., 1882, 2. s., x, 63, 213.

¹² Shattock, S. G. *Trans. Path. Soc.*, Lond., 1886, xxxvii, 287.

¹³ Still. *Ibid.*, 1898, xlix, 155.

frequency
 persistence of fetal mesoblastic stroma and not inflammatory. In other words, the change is a malformation, and is therefore not necessarily progressive. Hence if death does not occur in early life, the cystic change may be found as a persistent condition in the adult cases. The close association with cystic kidneys, also, according to Shattock's view, a malformation, is thus rendered intelligible. It is also significant that other malformations may coexist. Thus, in one case the remarkable association of polydactylism, occipital meningocele, and webbed toes was found; in another a misplaced kidney; in another an undescended testis;¹ and in several others polydactylism. These external malformations are not met with in adult cases, and are not constant in the cases fatal at birth. It may reasonably be supposed that the cases in which the developmental defects are comparatively slightly marked persist to adult life. Moschcowitz² described aberrant bile-ducts in the fibrous tissue of the portal spaces of cystic livers, which were not present in normal livers though they were in livers from cases with cystic kidneys. This observation might be considered to support Still's hypothesis. But my impression is that what Moschcowitz calls aberrant bile-ducts are the microscopic cysts of a cystic liver.

Some doubt has been expressed whether the change is more allied to a new growth or to a malformation, and possibly it may be regarded as having an intermediate position between these two processes. Most writers accept Still's explanation, but personally I am not convinced that this view is more tenable than that cystic disease of the liver is due to some special form of fetal cholangitis and pericholangitis.

Clinical Picture.—Cystic disease of the liver may be suspected in a patient with greatly enlarged and probably cystic kidneys who has vague uraemic symptoms and considerable enlargement of the liver. In rare instances the cysts in the liver may be so large as to imitate hydatid or ovarian cysts. In Schroeder's case the abdomen was so widely occupied by the cystic liver that double multilocular ovarian cysts were diagnosed. A single large cyst may imitate a dilated gall-bladder (Cleaver). ~~In practically all cases~~ symptoms pointing to the liver are absent, and death, if not due to some intercurrent affection, is from uraemia or cerebral haemorrhage.

In a woman, aged thirty-nine, who died under my care from rupture of a small aneurysm on the right vertebral artery, there were cystic kidneys, cysts in the liver, ovarian cysts, hydrosalpinges.

In Budd's³ and Blackburn's⁴ cases there was jaundice due to gall-stones. As far as I know, the adult cases do not shew malformations of the limbs.

The cystic kidneys may be felt in life and sometimes have been regarded as hydronephroses, or even as pyonephroses.

¹ Cases quoted by Still. *Trans. Path. Soc.*, Lond., 1898, xlix, 164.

² Moschcowitz. *Am. Journ. Med. Sc.*, Phila., 1906, cxxxi, 674.

³ Budd. Quoted by Blackburn, *loc. cit.* p. 250.

⁴ Blackburn. *Trans. Path. Soc.*, Lond., 1904, lv, 203.

1) Letulle and Verhac called the condition a dyscaryoma, and Von Meyenburg considered that the cysts were bile channels communicating with the liver cells but not with the larger bile ducts.

Although the cysts increase in size as time goes on, there is always enough liver substance to carry on its functions, and

Meyenburg,

Beitr. z. path. Anat. u. z. allg. Path., Jena, 1918, Lxiv, 477.

LECÈNE figures an adenoma, ¹
isolated and green in colour,
the size of two fists.

LECÈNE. Rev. de gyn. et de chir. abdom., Paris,
1912, XIX, 555

A woman aged thirty-five was admitted into St. George's Hospital with pain of one week's duration on the left side of the abdomen, where a soft, obscurely fluctuating tumour could be felt in the region of the kidney. There was pus in the urine, but no fever or leucocytosis. There had been dragging pain in the back from time to time, and increased frequency of micturition, especially at night, for nine years. An exploratory operation shewed that both kidneys contained numerous cysts of considerable size, and that the liver also contained many cysts. A small piece of the liver containing some small cysts was removed. Microscopically I found that the cyst walls were composed of well-formed fibrous tissue and that in the immediate neighbourhood there was fibrosis around the portal spaces. No epithelial or other lining could be found in the cysts.

In the congenital case described by Kanthack and myself the infant, aged one month, was universally oedematous, had a large quantity of albumin in the urine, and was extremely drowsy, as if uraemic; and 3 previous children had died in a similar way soon after birth.

The treatment, if the condition be suspected, is that of chronic renal disease, the object being to prevent uraemia. Opening the cysts in the course of laparotomy has been done, but is useless, and should be avoided if the condition is recognised.

ADENOMAS

THE subject of adenoma may be considered under the two heads of (I) single adenoma, (II) the so-called multiple adenomas which are nearly always associated with portal cirrhosis of the liver.

SINGLE ADENOMA.—An innocent encapsulated growth of epithelial cells may occur in the liver, but is decidedly rare; pathologically it is of great interest, but clinically it seldom attracts attention.

These adenomas may be divided according to their structure into: (I) those composed of liver cells; (II) those derived from the bile-ducts; (III) those due to the inclusion of adrenal "rests."

I. Solitary Adenomas Derived from the Liver Cells.—An adenoma composed of liver cells, apart from the multiple growths of this kind seen in association with cirrhosis, is rare. Such growths may be spoken of as "acinous adenomas" in contradistinction to those derived from the bile-ducts, or as "solitary adenomas" in order to distinguish them from multiple adenomas. They occur equally in the two sexes, and at any age, from six months to sixty-nine years (Barbacci¹). or mass v

An adenoma, measuring 8 inches in diameter, in the left lobe of the liver gave rise to a tumour palpable during life in a patient in St. Thomas's Hospital.² A large adenoma, $6\frac{3}{4}$ inches in diameter, in a lardaceous liver

¹ Barbacci. *Clin. mod.*, Milano, 1900, vi, 297.

² *St. Thomas's Hosp. Rep.*, 1904, xxxiii, 83.

shewed the lardaceous change (Shattock¹). Muir² described an adenoma measuring $4 \times 3 \times 3$ inches in a girl aged nine years; it was composed of liver cells irregularly arranged; there were no bile-ducts; and Milne³ an adenoma 3 inches in diameter in a child of six months. Mahomed⁴ described a localised collection of cells surrounded by a fibrous capsule embedded in the liver which was "nutmeg"; the tumour did not share in this general change. I have seen a similar specimen. There is a specimen (2223b) of a single necrotic adenoma in St. Bartholomew's Hospital Museum. Specimens have also been described by Engelhardt⁵ and others.

Possibly these tumours may be due to a piece of liver substance which was separated during fetal life from the main liver, becoming subsequently embedded in the organ. Small projections of liver substance, miniature lobes, are occasionally seen on the under surface of the liver; if these become implanted in the substance of the liver, the appearance of an encapsulated adenoma, composed of liver cells, would be produced.

Cristiani⁶ refers to the existence of multiple nodules of hepatic tissue embedded under Glisson's capsule, which have been explained as congenital and due to the inclusion of tiny lobes. Pepere⁷ supports the congenital origin of solitary adenoma and describes a case in which there were, in addition to one in the liver, innumerable minute encapsulated masses of liver tissue scattered over the peritoneum and omentum.

A simple adenoma is nearly always solitary; it is very rare that several are seen in the same liver. Multiple adenomas are nearly always accompanied by multilobular cirrhosis, and may be regarded as secondary to that condition and in the light of compensatory hyperplasias of the liver cells. ~~A few examples of multiple adenoma without pre-existing cirrhosis are referred to on page 459.~~

In exceptional cases a solitary adenoma is found in a cirrhotic liver. Among twenty cases of solitary adenoma collected by Caminiti,⁸ four were associated with cirrhosis (Jona,⁹ Delaunay,¹⁰ and two of his own). Possibly in some cases the association is a mere coincidence. Delaunay's case of a columnar-celled growth being probably of this nature. But in most cases it is probable that a "solitary adenoma" in a cirrhotic liver is only the initial stage of the multiple adenoma in cirrhosis. I have seen two cases bearing this interpretation.

¹ Shattock *Proc. Roy. Soc. Med.*, Lond., 1910, iii (Path. Sect.), 153.

² Muir, R. *Journ. Path. and Bacteriol.*, Cambridge, 1908, xii, 303.

³ Milne. *Ibid.*, 1909, xiii, 348.

⁴ Mahomed. *Trans. Path. Soc.*, 1877, xxviii, 144.

⁵ Engelhardt. *Deutsch. Arch. f. klin. Med.*, 1898, lx, 607.

⁶ Cristiani. *Journ. d'anat. et physiol.*, 1891, xxvii, 271.

⁷ Pepere. *Arch. per le sc. med.*, 1902, xxvi, 117.

⁸ Caminiti. *Arch. f. klin. Chir.*, 1903, lxi, 630.

⁹ Jona. *Gazz. d. osp.*, 1901, xxii, 88.

¹⁰ Delaunay. *Bull. Soc. Anal.*, Paris, 1876, li, 241.

Large Adenomas have also been recorded,
eg G. G. Turner, F. Reed, Starr

^ | Dévé described four simple adenomas in
the same liver, and suggested the name
massive adenomas

DÉVÉ. NORMANDIE méd., ROUEN, 1913, XXIX, 157.

or reddish-
brown.

of varying size with little definite arrangement, without bile ducts, but capillaries and sometimes angiomatous tissue. In some cases tubular adenomas not derived from the bile ducts have been reported. These benign adenomas have been called a trabecular adenoma with a tendency to become carcinomatous, and resembling histologically carcinoma with cirrhosis has been described (LECENE); this has also been termed hepatoma (Ramon, Geraudel, et Monier-Vinard)

Clinically, these adenomas may imitate hydatid cysts or primary carcinoma, and it is probable that cases of primary carcinoma of long duration, such as Ribadeau-Dumas and Langeron's of 5 years, was originally a trabecular adenoma

Morbid Anatomy.—The tumour, often the size of a walnut, projects from the surface of the liver, usually from the right lobe. It is ~~is~~ yellow ~~with~~, ~~or~~ greenish white on section, and of the same consistence as normal liver, but usually does not share in any change, such as chronic venous engorgement, affecting the liver as a whole. It may shew much necrosis (Fig. 59). In the liver of a man with advanced pulmonary tuberculosis a single adenoma so closely resembled a tuberculoma that a microscopical examination was necessary to decide its nature. The presence or absence of a capsule depends on the rate of growth of the adenoma.

Tumour on
colours, &
may be

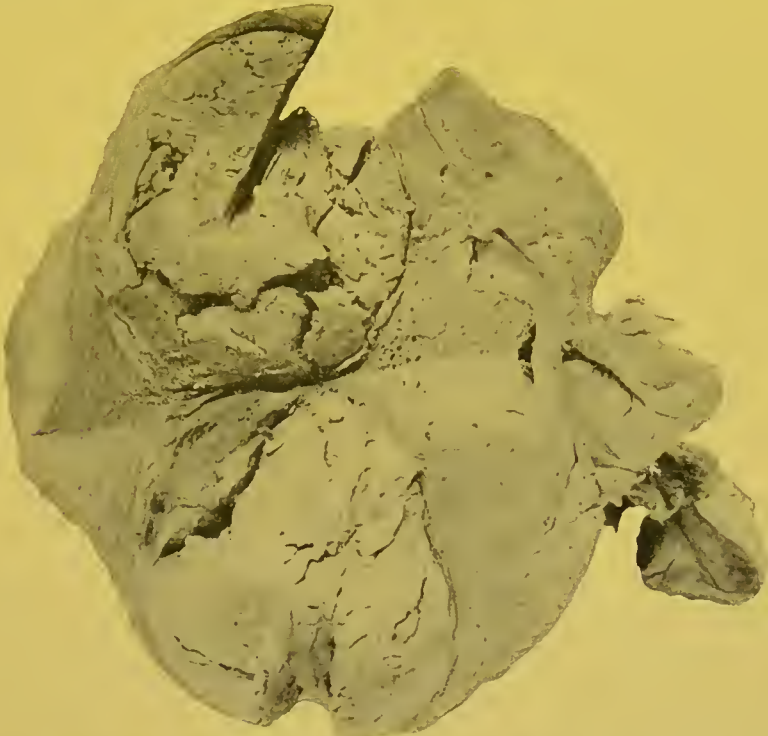


FIG. 59.—Large single adenoma of liver. (From a photograph kindly lent by Dr. I. Strauss.)

Microscopically the tumour is composed of liver cells which may, probably when the tumour is of some standing, be so modified as to form tubules lined by cubical epithelium; the structure approaches that of carcinoma with cirrhosis. Plugs of coagulated material containing bile-pigment may be present. The cubical character of the cells distinguishes this form of adenoma from the adenomas derived from the bile-ducts. In most cases the solitary adenoma derived from the liver cells is composed of cells of various sizes, but generally resembling liver cells. There is no definite arrangement, but there are capillaries and some strands of fibrous tissue running through the tumour.

II. Adenomas Derived from the Bile-ducts.—A papilloma springing from the inside of the extrahepatic bile-ducts would come under this heading, but is dealt with elsewhere (*vide* p. 687). Reference will be

made here to tumours arising from the intrahepatic bile-ducts, indenting and displacing, but not invading, the surrounding liver substance; they may be described as tubular adenomas lined by columnar cells. Cagnetto¹ described an adenoma with ciliated epithelium. It is possible that similar adenomas may be derived from the mucous glands in the walls of the larger bile-ducts. They may be single or multiple. λ

A *single adenoma* derived from the bile-ducts may become cystic; Leppmann² collected nine cases of this kind; such an adenoma may imitate malignant disease or hydatid cyst of the liver, a floating kidney, or an ovarian cyst (Kauffmann³). The nature of such tumors can only be determined by laparotomy. Cases of this kind have been recorded by Keen, Shattuck, Schmidt, Walker Hall and Brazil.⁴ λ

Keen⁵ removed a cystic adenoma, thought to be derived from the bile-ducts, from a woman aged thirty-one in 1891, who was alive in 1899. Clinically it simulated a floating kidney. Shattuck's⁶ case is well worth quoting: A woman aged sixty-three presented a tumour reaching from the right costal arch to the iliac crest. It was smooth, not tender, and presented a fluctuating area in the centre. At the laparotomy a cyst containing a gallon of clear fluid was found and drained. After some time bile came away from the sinus. A second operation was followed by death from cardiac failure. At the necropsy the cyst arose from the liver near the falciform ligament and displaced the liver downwards. Microscopically the cyst wall contained numerous ducts and minute cysts, and it was regarded as a cystadenoma and not as a simple retention cyst.

It is quite possible that a large adenoma of the bile-ducts is sometimes regarded as primary carcinoma of the liver.

Peugniez⁷ operated upon a woman aged fifty-nine for a tumour diagnosed as a gall-bladder; an encapsuled tumour the size of the fist was removed and the patient recovered. The tumour was regarded as a primary massive carcinoma of the liver, but the description and figures given are quite compatible with the view that it was a large adenoma of the bile-ducts, as in Keen's case.

Multiple adenomas derived from mucous membrane of the bile-ducts have been recorded (v. Hippel⁸). They may undergo cystic change, as in a remarkable case of Siegmund's⁹ in a woman aged sixty-five. As has been pointed out (*vide* p. 453), multiple cystic disease of the liver was regarded ~~by Malassoz, Claude, and others~~ as a fibro-adenoma of the bile-ducts.

III. Adenomas Due to Included Accessory Adrenals.—Schmorl,¹⁰

¹ Cagnetto. *Arch. per le sc. med.*, Torino, 1910, xxxiv, 495.

² Leppmann. *Deutsche Ztschr. f. Chir.*, 1900, liv, 446.

³ Kauffmann. *Zentralbl. f. Gynäk.*, 1907, xxxi, 913.

⁴ Walker Hall and Brazil. *Med. Chron.*, Manchester, 1903-4, xxxix, 243.

⁵ Keen, W. W. *Ann. Surg.*, 1899, xxx, 267.

⁶ Shattuck. *Boston Med. and Surg. Journ.*, 1900, cxlii, 427.

[c] ⁷ Peugniez. *Bull. Soc. Anat.*, Paris, 1902, lxxvii, 456.

⁸ v. Hippel. *Virchows Arch.*, 1891, cxxiii, 473.

⁹ Siegmund. *Ibid.*, 1889, cxv, 155.

¹⁰ Schmorl. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1891, ix, 523.

Out of 19 adenomas of the bile ducts 15 were single
and 4 multiple (Gordinier and Sawyer).

1) A Evans

Gordinier and Sawyer Amer. Journ. Med. Sc., Phila., 1913, CXLV, 258.

A. EVANS. Proc. Roy. Soc. Med., 1920, XIII (Clen. Sect.) 86; Brit. Journ. Surg., 1921, IX, 155

Weller reviewed the subject of
heteropia of the adrenal on
the liver and found 3 cases
in 800 necropsies.

An hepatic hypernephroma
has been associated with
Recklinghausen's disease
(SARLMANN)

Weller, C.V. Am. Journ. Med. Sci., 1925, CLXIX, 69

SARLMANN Virchow's Arch., 1913, C
422

Oberndorfer,¹ Beer,² and Peperc³ shewed that accessory adrenals are sometimes embedded in the liver. Schmorl found them in 4 out of 510 bodies, and Beer 6 times in 150. Encapsuled tumours of the liver derived from included suprarenal "rests" have been described by Schmorl and de Vecchi,⁴ and it is probable that the development of simple adenomas in accessory suprarenals implanted in the liver is not very rare. Clinical symptoms are exceptional; Flemming⁵ described a case in which an adenoma compressed the common bile-duct. Primary malignant tumours of the liver may arise in an accessory suprarenal (*vide* p. 481).

MULTIPLE ADENOMAS OF THE LIVER

Synonyms: Nodular Hyperplasia; Nodular Hepatitis; Hepatoma.

Multiple adenomas of the liver due to multiplication or hyperplasia of the liver cells are usually associated with cirrhosis of the liver, probably because cirrhosis is the commonest disease which destroys the liver cells and renders a compensatory hyperplasia necessary. Nodular hyperplasia may be met with in the absence of cirrhosis, as in some cases of malarial infection, in subacute atrophy, and in chronic venous engorgement of the liver.

A man aged thirty-seven died in St. George's Hospital in 1903 with advanced pulmonary tuberculosis and tuberculous peritonitis. The liver was at first thought to be stuffed with caseous tubercles. Microscopically these white areas were multiple adenomas; the liver shewed no cirrhosis.

As the result of injection of blastomycetes, Wlaeff⁶ produced adenomatous tumours in the livers of guinea-pigs. J. Bartel⁷ drew a distinction between multiple adenomas which are surrounded by a fibrous capsule, and nodular hyperplasia without any capsule.

Relationship of Multiple Adenomas and Cirrhosis.—Kelsch and Kiener,⁸ and more recently Dieulafoy⁹ and Engelhardt,¹⁰ believe that the cirrhosis and the adenomas are due to the same poison and are the concomitant results of proliferation of the framework and of the cells of the liver respectively. In the Fuegians as the result of eating mussels, which at certain periods of the year contain a chemical poison, the liver is enlarged from hyperplasia of the cells and subsequently becomes cirrhotic (Segers¹¹).

¹ Oberndorfer. *Centralbl. f. allg. Path. u. path. Anat.*, 1900, xi, 145.

² Beer. *Ztschr. f. Heilk.*, 1904, xxv, 381.

³ Peperc. *Monitore zoolog. ital.*, 1903, xiv, 267.

⁴ de Vecchi. *Virchows Arch.*, 1904, clxxvii, 133.

⁵ Flemming. *Brit. Med. Journ.*, 1911, ii, 1475.

⁶ Wlaeff. *Journ. de méd.*, Paris, 1901, p. 27.

⁷ Bartel. *Wien. klin. Wchnschr.*, 1904, xvii, 613.

⁸ Kelsch et Kiener. *Arch. de physiol.*, Paris, 1876, iii, 622.

⁹ Dieulafoy. *Manuel de path. intern.*, 1901, ii, 734.

¹⁰ Engelhardt. *Deutsches Arch. f. klin. Med.*, 1898, lx, 607.

¹¹ Segers. *Semaine méd.*, 1891, xi, 448.

Bring this into
our acute
diagnosis

Cornil and Ranvier,¹ Orth,² and Schmieden³ regarded the adenomas as secondary to the cirrhosis. Brissaud⁴ described multiple adenomas as a half-way house between cirrhosis and primary carcinoma, and the term "hepatoma" was suggested by Sabourin⁵ to describe the transitional stage between adenoma and carcinoma. Lancereaux⁶ and Marckwald⁷ took the extreme view that cirrhosis was due to irritation set up by the presence of the adenomas.

There is some confusion in literature between cirrhosis with multiple adenomas and primary carcinoma with cirrhosis. It appears that Sabourin, who uses the former term, is sometimes describing cases which Hanot and Gilbert would call primary carcinoma with cirrhosis. The innocent condition of multiple adenoma in cirrhosis may eventually pass into primary carcinoma. When this occurs, there will be evidence of infiltration of the walls of the portal or hepatic veins, or of secondary growths in the lungs or elsewhere. Muir,⁸ however, believes that no hard and fast line can be drawn between multiple adenomas in cirrhosis and primary carcinoma with cirrhosis, and that the first is potentially malignant from the outset.

Nature of Multiple Adenomas.—These multiple adenomas are usually associated with cirrhosis. Some reservation is necessary, since nodular hyperplasia or multiple adenomatous formations are found in other conditions (*vide* p. 459). The multiple adenomas ordinarily met with are exaggerations of the hobnails seen in portal cirrhosis, and represent a further stage of nodular hyperplasia. Multiplication of the more healthy liver cells occurs in common or portal cirrhosis and contributes to the size of the hobnails and to the increased weight of the liver in latent cirrhosis. It is when these hobnails undergo fatty degeneration and necrosis, and appear white on section, that they are particularly liable to attract attention, for when this change has occurred they do not, unless bile-stained, suggest cirrhosis, but resemble multiple new-growths or even caseous tubercles. Fatty change and necrosis of the hyperplastic nodules are particularly likely to occur when portal thrombosis complicates cirrhosis; hence the frequency with which portal thrombosis is recorded as associated with multiple adenoma, cancer with cirrhosis, etc. Thus in 15 cases of so-called adenoma of the liver analysed by Dr. Ll. Powell,⁹ no less than 9 had thrombosis of the (portal vein.

Those who regard the condition as one of primary carcinoma of the liver adduce the presence of hepatic cells in the portal vein and throm-

¹ Cornil et Ranvier. *Manuel d'histologie pathologique*, 1884, ii, 438.

² Orth. *Lehrbuch der path. Anat.*, 1887, quoted by Muir.

³ Schmieden. *Virchows Arch.*, 1900, clix, 290.

⁴ Brissaud. *Arch. gén. de méd.*, Paris, 1885, ii.

⁵ Sabourin. *Thèse de Paris*, 1881; *Rev. de méd.*, Paris, 1884, iv, 321.

⁶ Lancereaux. *Gaz. méd. de Par.*, 1868, 3. s., xxiii, 646.

⁷ Marckwald. *Virchows Arch.*, 1896, cxliv, 29.

⁸ Muir, R. *Journ. Path. and Bacteriol.*, Cambridge, 1908, xii, 287.

⁹ Powell. Unpublished Thesis for M.B. Cantab., 1895.

bosis as further proof of its malignant character. But the presence of some hepatic cells in the portal vein does not absolutely prove that the growth is malignant, for the hobnails, being poorly nourished and having by rapid proliferation outgrown their blood-supply, soften down and may discharge into the portal or hepatic veins, and so induce thrombosis. Microscopic examination of the thrombus shews blood-clot with debris and large fatty liver cells.

Delépine¹ drew attention to this discharge of softened adenomas into the portal and hepatic veins, and F. C. Turner² described liver cells and fragments of liver tissue in the portal veins of cirrhotic livers and suggested that it was due to damage of the vessel walls by the infective process present in both his cases.

The proliferation of the liver cells is a compensatory process and occurs without the production of any transitional cells. When this process of regeneration is in progress, pseudobile canaliculi are usually prominent objects microscopically, and they have in the past been thought to be part of the compensatory process; but the general consensus of pathological opinion is adverse to this view.

Compensatory hyperplasia of the liver cells occurs in the most diverse conditions, which all have in common, interference with the functional activity or destruction of the liver cells. The effects of removal of portions of the liver in animals have been investigated by Tizzoni, Ponfick,³ v. Meister,⁴ Floeck,⁵ Zadoc-Kahn,⁶ and others; and Milne⁷ has given a full account of the histology of regeneration of the liver in man. Proliferation begins and is most active, probably because nutrition is best there, in the liver cells at the periphery of the lobules.

When multiple adenomas in cirrhosis are seen at the necropsy of fatal cases of cirrhosis, the compensatory mechanism has in most cases broken down, and this is sometimes explained by thrombosis of the portal vein. The compensation may also be nullified by degenerative processes, fatty change, or softening in the hyperplastic hobnails, or by fibrosis spreading into them. No doubt the large size of livers in latent cirrhosis is partly due to this compensatory hyperplasia of the liver cells (see p. 196). Nodular cirrhosis is not very infrequent in cases fatal from pulmonary tuberculosis, and may be looked upon as a compensated cirrhosis. In such cases, if fatty degeneration attacks the hobnails, an appearance suggesting caseation results; it is quite possible that a naked-eye examination of the liver might result in a diagnosis of extensive tubercle or new growth of the organ.

¹ Delépine, S. *Trans. Path. Soc.*, Lond., 1890, xli, 362.

² Turner, F. C. *Ibid.*, 1884, xxxv, 22; and 1886, xxxvii, 262.

³ Ponfick. *Virchows Arch.*, 1899, cxix, 193.

⁴ v. Meister. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1893, xv, 1.

⁵ Floeck. *Deutsches Arch. f. klin. Med.*, Leipz., 1895, lv, 397.

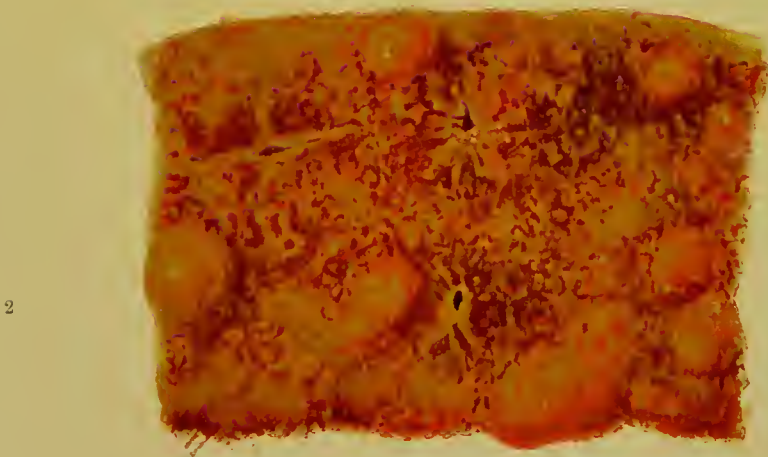
⁶ Zadoc-Kahn. *Arch. gén. de méd.*, Paris, 1897, clxxix, 165.

⁷ Milne. *Journ. Path. and Bacteriol.*, Cambridge, 1909, xiii, 127.

Morbid Anatomy.—The appearance of the liver is very striking and suggests multiple secondary new growths (*vide* Plate 5), gummas, or even caseous tubercle. The surface shews numerous projecting nodules, which, however, are not umbilicated. They are white on section, usually dry and friable, but may, especially when associated with portal thrombosis, be softened. The surrounding liver substance may be deeply congested, so that the contrast between the hobnails and the rest of the liver still further suggests secondary malignant disease. Adenomas in children with cirrhosis may be extremely prominent, and to the naked eye very closely resemble malignant disease; probably this active proliferation is part of a child's inherent power of repair and growth. The liver is usually enlarged, and sometimes to a very great extent. It is only rarely that it is actually smaller than natural. The conditions of hobnailed liver, nodular cirrhosis, and cirrhosis with multiple adenomas run into each other, and what one observer might speak of as extreme cirrhosis might by another be called cirrhosis with adenoma. The portal vein is frequently thrombosed, and microscopic examination of the clot may shew a few liver cells due to the discharge of one of the softened hobnails into the vein. Sometimes similar thrombosis is seen in the hepatic veins. The lymphatic glands in the portal fissure are not enlarged.

Microscopically the liver shews marked cirrhosis; the masses which to the naked eye suggest new-growth are altered liver cells surrounded by a fibrous capsule; the interstitial tissue contains pseudobile canaliculi and sometimes extravasated blood. In a hyperplastic nodule examined at an early stage the liver cells are larger than natural, in a good state of nutrition, with homogeneous protoplasm, and are undergoing proliferation, usually by direct nuclear division, but indirect nuclear division also occurs. This stage may be spoken of as nodular cirrhosis. In an early stage the naked-eye appearances are more striking than the microscopic. The first impression on looking at a microscopic section of nodular cirrhosis is often one of disappointment at finding little more than the changes of cirrhosis. The process of hyperplasia goes on in the periphery of the lobules. The liver cells around the "regeneration nodule" are often flattened ~~from~~ pressure and may become spindle-shaped. The normal arrangement of the hepatic lobule is lost, and tortuous columns of cells are seen which often tend to form irregular circles around the intralobular vein. The cells vary in size, some are smaller than normal, others are larger, and multinuclear cells are sometimes seen. Haemorrhage may occur into the adenomas or around them, and fatty change may appear in the cells forming the adenomas, especially when the portal vein is thrombosed. Fibrosis may extend into the substance of the adenomas.

Secondary Changes in Multiple Adenomas.—The fatty metamorphosis of the cells already mentioned may lead to softening down of the adenomas and the formation of the cystic spaces. The adenomas may discharge into the branches of the portal or hepatic veins and set up



1. SURFACE OF LIVER WITH NODULAR CIRRHOSIS.
The hobnails look like masses of secondary new-growth.

2. SECTION OF LIVER WITH NODULAR CIRRHOSIS.
Shewing engorgement of fibrous tissue and white colour, due to fatty degeneration of the liver cells
in the hobnails. Drawn by Dr. B. A. Wilson.

thrombosis. From vigorous proliferation of the cells in the adenoma the process may become carcinomatous (*vide* p. 474).

Clinical Aspect.—Since multiple adenoma is usually a result of cirrhosis, its age and sex incidence, its signs and symptoms, treatment, etc., are much the same as in that disease. It is found in a high proportion of cases of cirrhosis with thrombosis of the portal vein, and is therefore very frequently associated with ascites and haematemesis. An attempt has sometimes been made to establish a difference between the clinical features of ordinary cirrhosis and multiple adenomas, and the tendency has been rather to lay stress on the presence of hepatic pain and to present a picture approaching that of malignant disease of the liver. But no reliance can be placed on any such clinical differences. Hyperplastic tumours in subacute atrophy of the liver may reach a very large size; Barbacci¹ describes one as large as a fetal head; and Milne² mentions two cases in which operation for an abdominal tumor had been performed.

ANGIOMA AND CAVERNOMA

Synonym: Naevus.

AN angioma or haemangioma is a true tumour with a new formation of arterioles; a cavernoma is a telangiectasis or dilatation of existing vessels; both occur in the liver (Adami³). The liver is more often the seat of these formations than any viscus in the body, but they are not very common in the liver; Lancereaux⁴ saw 25 cases, and Adami 20 in 1400 necropsies. They are more frequent in the livers of cats. Hanot and Gilbert⁵ say they are commoner in men, Thoma⁶ that they are more frequent in women. They may be congenital and have been seen in fetuses, though this is exceptional. Veeder and Austin⁷ collected 12 cases of solitary angiomas in infants, multiple angiomas are rarer. Usually they are found in old persons, and are then more probably acquired and may be due to a combination of local congestion of the hepatic vessels and atrophy of the liver cells. They are generally quite small. Large tumours are very occasionally seen.

In Fillipini's⁸ case there was a tumour as large as an adult's head in the left lobe of the liver in a woman aged twenty-two. In Mantle's case⁹ the

¹ Barbacci. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1901, xxx, 45.

² Milne. *Arch. Int. Med.*, Chicago, 1911, viii, 639.

³ Adami. *Principles of Pathology*, 1911, ii, 488.

⁴ Lancereaux. *Traité des maladies du foie et du pancréas*, 1899, p. 528.

⁵ Hanot et Gilbert. *Études sur les maladies du foie*, p. 315, 1888.

⁶ Thoma. *Pathology*, English Transl. by Bruce, i, 553, 1896.

⁷ Veeder and Austin. *Am. Journ. Med. Sc.*, Phila., 1912, cxliii, 102.

⁸ Fillipini. *Polietin.*, 1901; *Vide Epitome, Brit. Med. Journ.*, 1901, ii, No. 94.

⁹ Mantle. *Brit. Med. Journ.*, 1903, i, 365.

tumour which had been growing for two years, in a man aged thirty-three years, was thought to contain 8 pints of blood.

They may be multiple, but more often are single. As many as 42 (Veeder and Austin) have been seen in the same liver. Of Schmieden's¹ 32 cases, 18 were single, 14 multiple. Angiomas may be found at the same time in other abdominal viscera and elsewhere.

In Payne's² case there were exceptionally large cavernous angiomas in the liver, which weighed 6 pounds, and angiomas in both ovaries and both adrenals; in Petroff's³ case there were angiomas in the liver and in both adrenals. In Devic and Tolot's⁴ case there were 30 angiomas in the liver, and others in the spleen, fat around the left kidney, mediastinum, left breast, skin of the back, and an angiosarcoma of the brain.Λ

Morbid Anatomy.—They are usually immediately under the capsule, and often near the edge of the liver, on the convexity or in the neighbourhood of the falciform ligament. After death they become partially empty and are therefore slightly depressed below the level of the surrounding liver substance. In exceptional cases they are pedunculated.Λ Lancereaux figures a pedunculated angioma attached to a liver which also contained other angiomas; and Journiac⁵Λ also described this condition. They are round or wedge-shaped, with the base directed outwards and the apex inwards. On section they have a honeycombed appearance when the blood has been removed, like that of erectile tissue of the corpus cavernosum penis or of the placenta.Λ They are dark red in colour; occasionally the surrounding liver substance is darkened by infiltration with blood pigment. They are sometimes encapsuled or encysted, and in connexion with this it is interesting to note that Berard⁶ suggested that they were encysted splenic "rests." In large cavernous tumours there is usually a fibrous capsule; in smaller specimens there is often none, and the cavernous tissue is in immediate contact with the liver cells. The encapsulation is probably a secondary process, as in other innocent tumours. The capsule may shew calcification. The large angioma removed by Cripps⁷ was so extensively calcified that until the microscopical examination it was thought to be an ossifying sarcoma. There is considerable difference of opinion as to the connexions of these tumours with the vessels in the liver; they have been said to be connected with the veins only, or to be in free communication with the hepatic artery and with the portal and hepatic veins (Virchow). Probably the blood supply varies in the different forms of angioma.

¹ Schmieden. *Virchows Arch.*, 1900, clxi, 373.

² Payne, J. F. *Trans. Path. Soc.*, 1869, xx, 203.

³ Petroff. *Bolnich. Gaz. Botkina*, St. Petersburg, 1899, No. 30; abstract in *Rev. de méd.*, Paris, 1901, xxi, 920.

⁴ Devic et Tolot. *Rev. de méd.*, Paris, 1906, xxvi, 254.

⁵ Journiac. *Arch. de physiol. norm. et path.*, Paris, 1878, 2. s., vi, 37.Λ

⁶ Berard. *Bull. Soc. Anat.*, Paris, 1828, p. 9.

⁷ Cripps, W. Harrison. *Brit. Med. Journ.*, 1903, ii, 18.

1) In Major and Black's case ^{the liver containing} a cavernous angioma ^{ten times the normal and} of ~~the liver~~ weighed half the
 entire weight of the patient, there were 2 angiomas in the skull and multiple
 cysts in the adrenals. Malignant changes may supervene (Wintermütz and Boggs)

1) A pedunculated angioma with a diameter of 5 inches, ^{and adherent to the gall-bladder} was successfully removed from a
 woman by Mr. Fedden (St. George's Hosp. Museum Series IX, 177^E).

1) ~~Mac~~ MacCallum, Rubin

In Gatewood's case there was a central cavity, & a few
~~spaces~~ of the blood-spaces contained phleboliths.

Wintermütz and Boggs. Johns Hopkins Hosp. Bull., Baltimore, 1910, XXI, 203.

Major and Black. Am. Journ. Med. Sc., Phila., 1918, CLVI, 469

MacCallum, W.G. Textbook of Pathology, 901, 1917

Rubin. Am. Journ. Obst., 1918, LXXVII, 273.

Gatewood. Trans. Chicago Path. Soc., 1912, VIII, 312.

There may be evidence of blood-
formation (Mac Curdy, Moise)

Moise. Bull. Johns Hopkins Hosp., Baltimore, 1920, X
3

There does not seem to be any tendency to malignant (endotheliomatous) change in them.

Besides the pigmented or "melanotic" and the encysted angiomas, another form is described—the fibrous angioma—in which the trabeculae increase markedly in thickness and thus lead to obliteration of the cavities or to its cure.

Histology.—The cavernoma, or ordinary hepatic blood-containing formation, shews a communicating meshwork of spaces containing red blood-corpuscles. The walls of the spaces are composed of fibrous tissue with some young connective-tissue cells and elastic fibres. Smooth

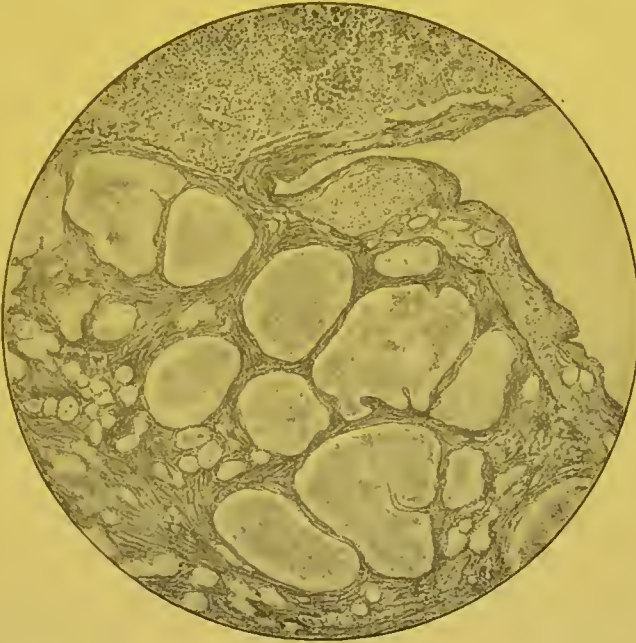


FIG. 60.—Drawing of cavernoma of the liver, shewing spaces containing coagulated blood with fibrous alveolar walls. It is encapsuled. $\times 21$.

muscle fibres are described in some specimens. The spaces are lined by flattened endothelial cells covering the fibrous trabeculae. The structure is therefore that of cavernous tissue. The tumour may be separated from the liver cells by fibrous tissue which serial sections prove to be continuous with Glisson's capsule. In many specimens there is no limiting capsule and the blood-spaces are in direct contact with the liver cells. Bile-ducts and liver cells may thus appear to be embedded in the tumour. Pigment granules may be found in the fibrous trabeculae as well as in the surrounding liver cells; Hanot and Gilbert¹ give an illustration of this under the title of "melanotic angioma."

The haemangioma or true tumour may be entirely composed of newly formed arterioles.

¹ Hanot et Gilbert. *Études sur les maladies du foie*, p. 341, 1888.

Secondary Changes.—The blood may clot in the cavernous spaces and the endothelium may then creep over the remains of the clotted blood. When the blood-supply is interrupted by thrombosis, the cavernous tissue may become modified so as to contain serous fluid and imitate a lymph-angioma. In other cases the fibrous framework of the tumour may proliferate and compress and eventually obliterate the blood-spaces; in other instances hyaline degeneration may occur in the fibrous stroma.

Pathogeny.—As already mentioned, two forms occur in the liver: (i) The cavernoma, which is the commonest, due to dilatation of existing blood channels. This is due to congestion of the liver and atrophy of the hepatic cells. These telangiectases are usually acquired, and are seen in the atrophied livers of old persons; but some are congenital. (ii) Angioma or haemangioma, a real tumour or blastoma, due to the ~~new formation of arterioles.~~ They show proliferation and power of independent growth.

Clinical Aspect.—In the majority of cases no symptoms can be ascribed to the presence of angiomas in the liver. It has been suggested that murmurs or venous hums heard over the hepatic region are sometimes produced in this way. In exceptional examples they have reached a considerable size (Steffen,¹ Chervensky,² Mantle, Cripps,³ McWeeney⁴).

In Petroff's⁴ case of a woman aged thirty-eight years with symptoms of Addison's disease, jaundice was found to be due to the pressure exerted by a large angioma of the liver on the bile-ducts. ~~There were cavernous angiomas in both suprarenals.~~ In Tédénat's⁵ case a fibrous angioma compressed the right hepatic and the cystic ducts and gave rise to jaundice, colic, and distension of the gall-bladder.

In some cases the condition has been diagnosed as hydatid or merely as a doubtful tumour of the liver.

I am indebted to Dr. Seymour Taylor for the notes of a man with a tumour in connexion with the liver which closely imitated a hydatid cyst; it was operated upon, and when exposed, still resembled a cyst; on puncture it bled profusely at every point. The patient left the hospital well.

In Sheppard's⁶ case there was marked ascites, probably due to the angioma. Intraperitoneal haemorrhage from rupture of a large hepatic cavernoma has been reported (Roggenbau⁷); A McWeeney's⁸ case was fatal from haematemesis, for which no cause could be found.

The prognosis is fairly good in the cases which are operated upon, which are the only ones which can be diagnosed with certainty during life.

Treatment.—As it is only exceptionally that hepatic angiomas give

¹ Steffen. *Jahrb. f. Kinderh.*, 1882, n.f., xix, 348.

² Chervensky. *Arch. de physiol.*, 1885, ii, 553.

³ Cripps, W. Harrison. *Brit. Med. Journ.*, 1903, ii, 18.

⁴ Petroff. *Bolnichn. Gaz. Botkina*, 1899, No. 30; Abstract in *Rev. de méd., Par.*, 1901, xxi, 920.

⁵ Tédénat. *Arch. gén. de méd.*, Paris, 1904, i, 579.

⁶ Sheppard. *Bristol Med.-Chir. Journ.*, 1907, xxv, 46.

⁷ Roggenbau. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1910, xlix, 313.

⁸ McWeeney. *Journ. Path. and Bacteriol.*, Cambridge, 1912, xvi, 401.

1) proliferation of the remains of
vascular embryonic tissue.

1) Major and Black.

ALIVISATO's case imitated gastric carcinoma, as did Wakeley's in which
a ~~hemangioma~~ in the left lobe caused obstruction of the cardiac orifice.

1) ; this has been recorded in an infant one week old (HAMMER).

WAKELEY, J. P. G. Brit. Journ. Surg., Bristol ¹⁹²⁴⁻ 1925, XII, 590
ALIVISATO. Bull. et mém. Soc. méd. des hôp. de Paris, 1920, 3^e sér., ¹⁹²⁰ XLV, 1191.

Hammer. Ztschr. f. Geburtsh. u. GYNÄK. ¹⁹²⁰ LIII

rise to any signs or symptoms, the question of treatment rarely arises. As the presence of a large angioma would imitate a tumour of the liver, the only method of treatment is surgical, but there is considerable danger of profuse haemorrhage. If the tumour was thought to be an angioma, electrolysis might be tried. Keen,¹ in a list of 75 cases in which resection of the liver has been done for neoplasms, refers to 4 cases of angioma thus treated. In 1904 Tédénat quoted 6 cases in which excision had been carried out.

OTHER INNOCENT TUMOURS

Lymphangioma.—Maresch² described a pedunculated lymphangioma, diagnosed as an ovarian cyst, which was removed from the right lobe of the liver of a girl aged five years. It is conceivable that a tumour of this kind might result from degenerative changes in an angioma of the liver.

Myxoma.—A very large growth in the liver of a patient who had previously had a tumour removed from the breast by Nunn,³ was described by the Morbid Growths Committee of the Pathological Society as a myxoma. Though probably a myxo-sarcoma, this specimen has often been referred to as a myxoma of the liver. A few other cases of myxoma have been described, but it seems probable that they are allied to sarcomatous rather than to innocent tumours. Cornil and Cazalis⁴ described a primary myxoma in the liver of a child of nine months.

Fibroma of the liver has been described in a few cases, but caution must be exercised in accepting their existence. In infants this condition may be a manifestation of congenital syphilis and belongs to the group of cases described by Marchand.⁵ Luschka's⁶ case of fibroma in a child one month old was probably of this nature. It is possible that other cases would be more correctly described as fibro-sarcomas. It is conceivable that an angioma might undergo fibrotic atrophy and eventually form a small fibrous tumour. Small fibromas, like those seen in the medulla of the kidney, occur in the liver and enclose bile-ducts; Genewein⁷ considers that they are not tumours in the ordinary sense of the term but fetal malformations, and speaks of them as hamartoma fibrocanaliculare.

Lancereaux⁸ described a fibroma infiltrated with calcareous salts, in a woman aged twenty-eight years. On the under surface of the right lobe of the liver of a woman aged fifty-six Chiari⁹ found a fibroma the size of an egg.

¹ Keen. *Ann. Surg.*, 1899, xxx, 276.

² Maresch, R. *Ztschr. f. Heilk.*, 1903, xxiv, 39.

³ Nunn, T. W. *Trans. Path. Soc.*, Lond., 1873, xxiv, 120.

⁴ Cornil et Cazalis. *Compt. rend. Soc. Biol.*, Paris, 1874, 5. s., iv, 22.

⁵ Marchand. *Centralbl. f. allg. Path.*, 1896, vii, 273.

⁶ Luschka. *Virchows Arch.*, 1858, xv, 168.

⁷ Genewein. *Ztschr. f. Heilk.*, Wien u. Leipz., 1905, xxvi (*Abt. path. Anat.*), 430.

⁸ Lancereaux. *Atlas d'anat. path.*, 1871.

⁹ Chiari. *Wien. med. Wchnschr.*, 1877, xxvii, 365.

Four calcified fibromas, varying in size from a nut to a grain of wheat, were found in the liver of a tuberculous woman (Pisenti¹). In a case of multiple neurofibromas the sympathetic nerves in the liver were beset with fibromas from the size of a bean to that of a millet seed (Ziegler²).

Lipoma.—Genuine fatty tumours do not occur in the liver. But what might be spoken of as a lipoma may be found indented on the surface, but outside the capsule, of the liver: these small tumours are in reality appendices epiploicae which have become detached from the colon and have come to rest between the diaphragm and the convexity of the liver.³ I have seen several examples of this condition. An encapsulated mass of fat of about the size of a nut is found in a depression on the convexity of the liver, which it tightly fits. The capsule of the liver passes between the fatty body and the liver substance and there is no vascular connexion between the fatty tumour and the liver.

Localised areas of extreme fatty change in the liver cells are sometimes met with; they probably depend on vascular obstruction and microbic activity, and are not likely to be mistaken for real fatty tumours. Turnbull and Worthington⁴ describe areas of atypical liver tissue, probably congenital anomalies, under the capsule, which are prone to fatty change. The fat which accompanies the obliterated umbilical vein in the falciform ligament sometimes increases in size so as to resemble a small fatty tumour. I have seen this in a woman who died after herniotomy.

Embryomas and teratomas are extremely rare in the liver.

Hanot and Gilbert⁵ refer to a cyst in the liver containing hair, cartilage, and fatty material. In a baby aged six weeks Misiek⁶ found a lobular tumour the size of a man's fist in the right lobe of the liver; it contained bone, cartilage, and cysts derived from the hypoblast, but no epiblastic elements, so it should be described as a teratoma rather than a dermoid cyst. During life it was thought to be a tumour of the right kidney. Pye-Smith⁷ described a teratoma adherent to, but not arising from, the liver in an infant one year old. During life the tumour had been tapped several times and the disease was regarded as cystic disease of the liver. It was an included fetus. Somewhat similar cases have been described by Philipp⁸ and v. Hippel.⁹

The secondary implantation on the surface of the liver of fragments of a ruptured ovarian embryoma, which is not a malignant metastasis, has been described.¹⁰

¹ Pisenti. Quoted by Pepere, *I Tumori maligni primarii del fegato*, p. 25, 1902.

² Ziegler. *Special Pathological Anatomy*, translated by Macalister, part ii, p. 342, 1884.

³ Rolleston. *Trans. Path. Soc.*, Lond., 1891, xlii, 160.

⁴ Turnbull and Worthington. *Arch. Path. Inst. London Hosp.*, 1908, ii, 52.

⁵ Hanot et Gilbert. *Études sur les maladies du foie*, p. 295, 1888.

⁶ Misiek. *Journ. Path. and Bacteriol.*, 1898, v, 128.

⁷ Pye-Smith. *Trans. Path. Soc.*, 1886, xxxvii, 499.

⁸ Philipp. *Jahrb. f. Kinderheilk.*, 1908, lxxviii, 353.

⁹ v. Hippel. *Virchows Arch.*, 1910, cci, 326.

¹⁰ Hulke, *Trans. Path. Soc.*, 1873, xxiv, 157; Latham, *ibid.*, 1899, l, 232.

The rarity of primary malignant
growths of the liver is remarkable
in the light of the organ's great
power of compensatory hyperplasia.

In 1924 Jaffe accepted only 48 examples

Sarcoma morans v. Minkowsky M. 42 Bm 1919. II, 378

Jaffe, R.H. Arch Int. Med., Chicago, 1924, XXXIV, 330

MALIGNANT TUMOURS

THIS subject will be considered in the following order: First the incidence and a detailed account of the morbid anatomy of primary malignant disease; then the incidence and a detailed description of the morbid anatomy of secondary malignant disease; thirdly, the general clinical picture; and, then, the points of distinction between the clinical manifestations of primary and secondary malignant disease of the liver.

PRIMARY MALIGNANT TUMOURS

Incidence. ~~Primary malignant tumours of the liver are rare.~~ Every case requires critical post-mortem investigation to make sure that it is not secondary to some obscure growth elsewhere, and that the tumour did not, in reality, start in the gall-bladder or larger bile-ducts.

In 18,500 necropsies at Guy's Hospital, Hale White¹ found 24 cases of primary carcinoma of the liver, or 0.13 per cent. Eggel² estimates that primary carcinoma occurs once in 2000 necropsies, or 0.05 per cent.

The numerical ratio between primary and secondary carcinoma of the liver has been placed between 1:20 and 1:40 (*vide* p. 487).

Primary sarcoma, in which endothelioma is included, of the liver is rarer even than carcinoma.

Leith³ collected 25 cases in 1897. In 1901 Vecchi and Guerrini⁴ critically examined 45 published cases of primary sarcoma of the liver, but only accepted 21 cases as undoubted examples of this rare condition. I have notes of 64 cases of reputed primary sarcoma, of which 32 occurred in patients over ten years of age and 32 under that age. These cases do not include those described as primary melanotic sarcoma (*vide* p. 485) or any which were probably examples of hepatitis due to congenital syphilis.

Sex.—Primary malignant disease of the liver seems to be more frequent in men than in women, and contrasts with primary carcinoma of the gall-bladder, which, like gall-stones, is infinitely commoner in women—gall-stones and carcinoma of the gall-bladder being both about four times more frequent in women than in men.

In 74 cases of primary malignant disease in adults (42 carcinoma, 32 sarcoma) which I have collected, 42 were males and 32 females. The male sex was more often affected by carcinoma; of the 42 cases, 29 being males and 13 females. In Eggel's collection of 163 cases of primary carcinoma 63 per cent were males. Among my 32 cases of primary sarcoma 19 were females and 13 males.

¹ Hale White. *System of Medicine* (Allbutt and Rolleston), 1908, iv, part i, 215.

² Eggel. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1901, xxx, 506.

³ Leith. *Lancet*, 1897, i, 170.

⁴ Vecchi and Guerrini. *Med. News*, N.Y. 1901, lxxix, 816.

Age.—Primary carcinoma of the liver occurs in or after middle life and is rare before forty years of age.

In 42 cases of primary carcinoma (males 29, females 13) the average age was 47·2 years, being 42·1 among the females and 49·3 among the males. In Egge's 163 cases the average age of the males was 53·11 years, and of the females 52·23. [^]

The earlier observers described cases of cancer or "scirrhus" in very young children, but most of them were probably sarcomatous or due to congenital syphilis.

Prescott¹ recorded a congenital carcinoma of the left lobe of the liver in an infant of five months, and Miller and Cleland² cases of primary carcinoma in male infants aged nine and seven months; but it is probable that these cases were endotheliomas.

In older children portal cirrhosis with multiple adenoma very closely resembles carcinoma. H. Fussell and Kelly's³ case of primary carcinoma in a girl aged sixteen years was regarded by Welch and Dock in this light.

18 Dr. Still has given me sections of a child's liver which looked exactly like malignant disease to the naked eye, but microscopically shewed cirrhosis with compensatory hyperplasia of the liver cells. Out of 29 reported cases of primary carcinoma of the liver in children, Philipp⁴ accepts as genuine 12, namely, those of Koltmann, Wulff, Pye-Smith, Birch-Hirschfeld, Engelhardt, Acland and Dudgeon, Schlesinger, Grawitz, Burt, Mattiolo, Plant, Lubarsch. Since then cases have been reported by Weaver,⁵ Karsner (2),⁶ and Mair.⁷ This making 16 in all. Primary carcinoma in a woman of twenty-two was recorded by Gilbert and Claude.⁷

Primary sarcoma may occur at almost any age. The oldest case to which I have a reference was seventy-three years, while congenital cases have been recorded. Primary sarcoma of the liver may, like sarcoma of the kidney, be divided into two categories: (a) those which occur in adult life and (b) those met with very early in life.

The average age of 32 cases occurring in patients over fifteen years of age was 47·53 years (males, 51·6 years; females, 44·7 years), or exactly the same as the average age for primary carcinoma of the liver. In addition to these 32 cases I have tabulated 32 cases of primary sarcoma of the liver under ten years of age.

In 1883 Picot⁸ collected 424 cases of malignant disease occurring under seventeen years of age; there were 13 of primary malignant disease of the

¹ Prescott. *Boston City Hosp. Rep.*, 1895, 6. s., 245.

² Miller and Cleland. *Arch. Path. Inst. London Hosp.*, 1906, i, 5.

³ Howard Fussell and Kelly. *Univ. Med. Mag.*, Phila., 1895, vii, 838.

⁴ Philipp. *Ztschr. f. Krebsforschung*, Berl., 1907, v, 326.

⁵ Weaver. *Guy's Hosp. Rep.*, 1909, lxiii, 225.

⁶ Karsner. *Arch. Int. Med.*, Chicago, 1911, viii, 238.

⁷ Gilbert et Claude. *Arch. gén. de méd.*, 1895, clxxv, 513.

⁸ Picot. *Rev. méd. de la Suisse Rom.*, 1883, iii, 660.

1/ As a ^{entire} curiosity reference may be made to primary carcinoma of the liver in 2 sisters aged 71 and 77 who died within a week of each other (HEDINGER).

1/ Report a Congenital malignant adenoma in a child of 4 months, Peiper a similar tumour in girl of 8½ months, Wollstein & Mixsell (child 9 months)

entire

(Cattle said to be the 4th case of Carcinoma in child)

1/ ~~Peiper~~ Peiper, Castle (a pedunculated tumour), Sansone, Griffith. DANCIE, 9

Hedinger. Centralbl. f. Path., 1915, XXVI, 385

Peiper. Jahrb. f. Kinderch., Berlin, 1912, LXXV, 690
Wollstein and Mixsell. Arch. Pediat., 1919, XXXVI, 268

MAIR. Journ. Path. and Bacteriol., Cambridge, 1912, XVI, 389. (also reported by
Lapage. Proc. Roy. Soc. Med., 1912, VI (Child. Dis. Sect), 45).

Castle. Surg., Gyn., and Obst., 1914, XVIII, 477.

Sansone, Androutsellis, et Bortland. Arch. de méd. expor. et d'anal. path., Paris, 1917, XXVIII, 430

Griffith. Am. Journ. Med. Sc., Phila., 1918, CLV, 79

DANCIE. Lancet, 1922, II, 228

Galt ibid 1922, II, 834

(~~Wolbach~~)[^]
(Wolbach and
Morse; Jaffe)

which have ^{since} ~~been~~ been
regarded as derived
from indifferent ~~cells~~
~~the~~ sympathetic nerve
cells, and so secondary
neuroblastomas in the
liver.

Wolbach, O. B. and Morse, J. L. Am. Journ. Child. Dis.
1918, xvi, 63.

JAFFE, R. H. Arch. Int. Med., Chicago, 1924, x,
39

liver. R. Williams¹ referred to 29 cases of primary malignant disease of the liver under the age of fifteen years, the majority of which were probably sarcomatous. Noeggerrath² described a case of primary malignant disease of the liver in a baby which interfered with delivery; a congenital case was also observed by Jacobi.³

In connexion with sarcoma occurring in early life a caution must be thrown out as to the error of regarding as sarcoma the lesions of congenital syphilis. Cases of intercellular cirrhosis in infants have been described as primary sarcoma and lymphosarcoma. A diffuse intercellular cirrhosis in fetal life is, like sarcoma, an embryonic connective-tissue growth, so that the two processes have much in common. Severe visceral syphilis in early life may give rise to haemorrhagic enlargement of the suprarenals. Such a case might be regarded as sarcoma of the liver with secondary growths. The presence or absence of the *Treponema pallidum* will decide the question. Secondary growths in the adrenals may occur in primary sarcoma of the liver (Guy's Museum, No. 1571). There appears to be a group of cases, with growths in both the liver and adrenals, in which it is difficult to determine the site of the primary tumour. Pepper⁴ collected 6 cases of congenital sarcoma of the liver and adrenals.⁵

Etiology.—This is not the place to discuss the large and unsettled problem as to the true cause of malignant disease or to consider the "parasitic" or "habit of growth" hypotheses on the question. There is, however, one form of primary carcinoma in the liver, namely, that which develops in a previously cirrhotic liver, which favours the view that carcinoma is due to the acquired habit of proliferation of the liver cells, which, starting as a compensatory hyperplasia and thus giving rise to multiple adenoma in cirrhosis, eventually becomes so excessive as to constitute carcinoma.

In a few cases a definite history of a blow on the abdomen preceding the onset of malignant disease is forthcoming and may possibly have played some part in starting cellular proliferation.

Morbid Anatomy.—*Situation of the Growth in Primary Malignant Disease of the Liver.*—Primary malignant disease of the liver usually arises in the right lobe, but occasionally is limited to the left lobe.

As a curiosity, reference may be made to malignant disease arising in a tongue-like lobe. In a case of calculous cholecystitis and pericholecystitis the pendulous lobe in connexion with the gall-bladder was found to be the site of primary carcinoma; at first sight it was thought to have started in the gall-bladder, but Roux⁵ satisfied himself that this was not the case.

On the other hand, the growth may infiltrate both lobes, so that it

¹ Williams, R. *Lancet*, 1897, i, 1328.

² Noeggerrath. *Deutsche Klinik*, 1854, vi, 496.

³ Jacobi. *Therapeutics of Infancy and Childhood*, p. 371, 3 ed., 1903.

⁴ Pepper. *Am. Journ. Med. Sc.*, 1901, cxxi, 287.

⁵ Roux. *Rev. méd. de la Suisse Rom.*, 1897, xvii, 114.

is impossible to decide where it started, or there may be multiple primary growths in both lobes.

The morbid anatomy will be considered under the two heads of Primary Carcinoma and Primary Sarcoma.

Forms of Primary Carcinoma.—It will be most convenient to consider seriatim the morbid anatomy of the various forms of carcinoma which may arise primarily in the liver.

I. Primary Massive Carcinoma (Synonym : “Cancer en Amande”) (Hanot and Gilbert).—There is a large white or yellowish tumour which

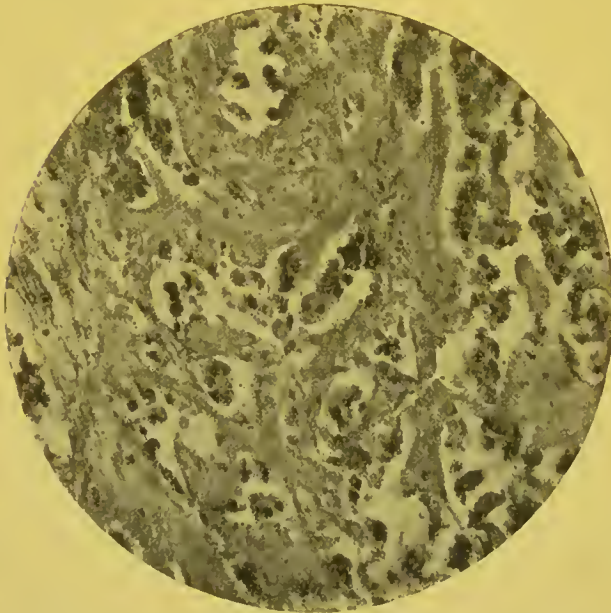


FIG. 61.—Photomicrograph of section of diffuse carcinoma of the liver. Shews a large quantity of hyaline fibrous tissue and groups of epithelial cells. (By S. P. Mummery, Esq.)

expands the liver like a shell around it. The surface of the liver is usually smooth ; but in some cases the growth may project or there may be irregularities from secondary growths ; in the latter event there may be adhesions between the liver and adjacent structures, such as the diaphragm and stomach. The growth is more or less localised, and forms a mass as big as a cocoanut or the fetal head. There may be secondary growths in the liver. It usually starts in the right lobe, but in rare instances

in the left lobe. According to Eggel, this form constitutes 23 per cent of the cases of primary carcinoma.

Structurally it is usually a polyhedral- or spheroidal-celled carcinoma of rapid growth, springing from the liver cells, or possibly from the cubical epithelium of the smaller bile-ducts. It has been suggested that embryonic relics derived from the duodenal diverticulum may be the starting-point of the growth. Exceptionally the growth is a columnar-celled carcinoma and has then arisen in connexion with the larger intra-hepatic bile-ducts.

Hanot and Gilbert¹ figure a giant-celled form of carcinoma in which the

¹ Hanot et Gilbert. *Études sur les maladies du foie*, p. 30, 1888, Paris.

^ Small masses of bile pigment may be seen in the tumour (Nicholson)

Nicholson, G. W. Guy's Hosp. Rep., 1927, Lxxi, 241.

(Goldzieher and Bokai Yamagiwa)
Many observers consider that
primary carcinoma of the liver
is multicentric in opposition
to Rebert's unicentric origin

Goldzieher und Bokai. Virchows Arch., 1911, CCIII, 75
Yamagiwa. Ibid., 1911, Cevi, 437
Rebert. Das Carcinom, 1911

largest cells measured as much as $100\ \mu$. Sokoloff¹ and Cagnetto² described cases with ciliated epithelium. C. Powell White³ described a primary carcinoma of the liver which softened down into a large cyst containing straw-coloured fluid; some of the cells measured 30 to $40\ \mu$ in diameter. A primary carcinoma of the liver resembling a chorion-epithelioma has been described (Cruickshank and Teacher⁴).

The fibrous stroma may shew hyaline change, but does not contain elastic fibrils (Wrench).⁵

II. Primary Infiltrating or Diffuse Carcinoma.—In this form the growth is diffuse, and extends more widely than in the previous category. The tumour may be comparatively slow growing and so hard as to simulate cirrhosis. The whole of one lobe may become transformed into a hard yellow growth; in such cases the liver may not be larger than natural.

Hilton Fagge⁶ described such a case in which the liver weighed $36\frac{1}{2}$ ounces and another weighing 62 ounces, but in his third case it weighed 186 ounces, and in Lee Dickinson's⁷ case, 102 ounces.

It may, however, be rapidly growing and soft, and extend throughout the whole of the liver, uniformly enlarging it.

The liver of a man aged sixty-four had a uniform hobnail appearance and on section was universally altered. It weighed 151 ounces and microscopically shewed a rapidly growing spheroidal-celled carcinoma.⁸

Structurally, the infiltrating form of carcinoma of the liver is nearly always spheroidal-celled, though a few cases shew a transition from a columnar-celled to a spheroidal-celled type. In the hard forms the epithelial cells may be scanty and embedded in wide tracts of fibrous tissue, which may shew advanced hyaline change. This is the rarest form of primary carcinoma of the liver. Eggel estimated that it occurred in 12 per cent of the cases.

III. Nodular or Multiple Primary Carcinoma.—The appearance of the organ is like that seen when it is occupied by secondary growths, the difference being that there is no primary growth.

It is quite possible that in some instances multiple adenomas with cirrhosis have been regarded as this form of multiple primary carcinoma, since the naked-eye resemblance is very close. In other cases it is possible that one of the multiple nodules was primary and that the others are secondary, but have grown more rapidly and so come to rival it in size. It is conceivable that these multiple primary carcinomas may in some

¹ Sokoloff. *Virchows Arch.*, 1900, clxii, 1.

² Cagnetto. *Arch. per le sc. med.*, Torino, 1910, xxxiv, 495.

³ White, C. P. *Brit. Med. Journ.*, 1899, ii, 1347.

⁴ Cruickshank and Teacher. *Journ. Path. and Bacteriol.*, Cambridge, 1910, xiv, 282.

⁵ Wrench. *Arch. Middlesex Hosp.*, 1905, v, 80.

⁶ Hilton Fagge. *Trans. Path. Soc.*, Lond., 1877, xxviii, 137.

⁷ Dickinson, L. *Ibid.*, 1894, xlv, 87.

⁸ Rolleston. *Ibid.*, 1894, xlv, 92.

instances be due to proliferating cells derived from a focus in the mucous membrane of the alimentary canal, which, though irritated, does not shew any carcinomatous growth. As an example of "secondary growths without any primary focus" attention may be called to the fact that squamous-celled carcinoma may arise in the inguinal glands of sweeps whose scrota, though covered with warts from the irritation of soot, do not shew any definite carcinomatous growth (Butlin¹).

This is the most frequent form of primary carcinoma of the liver. In Eggel's² collection of 163 cases it occurred in 104, or 64 per cent. In 41 cases from the Middlesex Hospital, however, it occurred in 15 or 36·5 per cent (Colwell³). The multiple tumours grow rapidly, are prone to degenerate, to ~~undergo~~ necrosis, and to become ~~infiltrated with extra-~~ ~~vascular~~ ~~blood~~. *haemorrhagic* *vascular blood*. Histologically, the growth is usually a spheroidal- or polyhedral-celled carcinoma. The cells are often of considerable size, and there is little interstitial connective tissue. The cells are probably derived from proliferation of the hepatic cells. In a few cases the growths are columnar-celled and are in all probability derived from the larger intrahepatic bile-ducts or possibly from mucous glands in their walls. In a case of multiple primary carcinoma shewing a transition from columnar- to spheroidal-celled growth, the origin was clearly from the bile-ducts (*vide* Fig. 62). ←

IV. Primary Carcinoma Developing in a Cirrhotic Liver (*Synonyms*: Primary Carcinoma with Cirrhosis; Malignant Adenoma; Cirrhosis Maligna; Cirrhosis Carcinomatosa).—This condition was described by Sabourin⁴ under the title of Cirrhosis with Multiple Adenoma, and as Hepatoma by Rénon, Géraudel, and Monier-Vinard⁵ who insist that it is not a carcinoma. "Hepatoma," also employed by Sabourin (p. 460), is a confusing title; Yamagiwa⁶ uses it for primary carcinoma of the liver. Hanot and Gilbert,⁷ who called it Carcinoma with Cirrhosis, state that a third of the cases of primary carcinoma of the liver are of this special variety. It occurred in 10 of the 41 Middlesex Hospital cases. It is probable that more than one condition has been described under this name. Some of the cases are probably that form of cirrhosis in which the hobnails are extremely well marked, and in which the hepatic cells in them have undergone a compensatory hyperplasia, or cirrhosis with multiple adenomas, and it is noticeable that in this class secondary growths are rare. This condition of nodular cirrhosis has a great naked-eye resemblance to multiple new-growths. The hobnails may undergo fatty degeneration, and may discharge their contents into the intrahepatic branches of the portal, or sometimes the

¹ Butlin, H. T. *Brit. Med. Journ.*, 1892, i, 1341.

² Eggel. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1901, xxx, 506.

³ Colwell. *Arch. Middlesex Hosp.*, Lond., 1905, v, 125.

⁴ Sabourin. *Thèse de Paris*, 1881; *Rev. de méd.*, Paris, 1884, iv, 321.

⁵ Rénon, Géraudel, et Monier-Vinard. *Arch. de méd. expér. et d'anat. path.*, Paris, 1910, xxii, 311.

⁶ Yamagiwa. *Virchows Arch.*, 1911, cxi, 437.

⁷ Hanot et Gilbert. *Études sur les maladies du foie*, p. 63, 1888.

1 The nodules are umbilicated
Perihepatitis may be present. The glands in the hilum are infected and metastasis usually occurs by the lymphatics.

This form occurs especially at the extremes of life, between 60 & 65 and in children (Parcelier and Fromaget).

Blumenau estimated that primary carcinoma was ten times more frequent in cirrhosis than in other conditions, occurring in 3.5 per cent. of 198 cases of cirrhosis; M.J. Stewart found it in 6 of 149 cases of cirrhosis or 4 per cent. (vide p)

Parcelier et Fromaget. Arch de méd. expér. et d'anat. path., Par., 1912, xxiv, 180.

Blumenau. Arch. f. Verdauungskrankh., 1920, xxvii, 1.

Stewart M.J. Brit Med Journ., 1922, li, 1066

hepatic, veins, and give rise to thrombosis; the presence of liver cells in the portal vein has been regarded by some as evidence that the change is carcinomatous, but without sufficient reason. In other cases of cirrhosis it seems probable that thrombosis of the portal vein is the

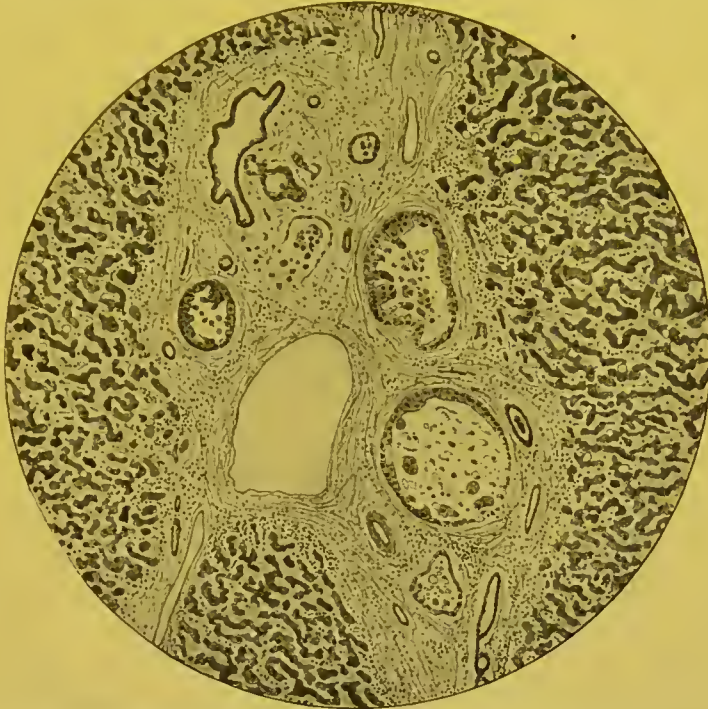


FIG. 62.—Pre-cancerous proliferation of the bile-ducts in multiple primary carcinoma. From a section kindly given me by Dr. L. S. Milne.

primary factor, and that this leads to necrosis and softening of the cirrhotic hobnails, which thus closely resemble masses of secondary new-growth.

Cirrhosis with compensatory hyperplasia of the liver cells forms a connecting link between cirrhosis, on the one hand, and carcinoma, on the other. Where the line separating the proliferation of the hepatic cells from carcinoma is transgressed, it may be difficult to determine, but that carcinoma may thus result is certain.

The relation of the carcinomatous growth to the fibrosis in carcinoma with cirrhosis has been regarded in the following lights:—

(a) That the cirrhosis and the carcinoma both develop at the same time and are due to irritation applied respectively to the interstitial connective tissue and to the cells of the liver (Hanot and Gilbert).

(b) That the carcinoma is the primary change, and that the cirrhosis is secondary to the irritation set up by the growth and is related to it in the same way that the interstitial tissue of a hard spheroidal-celled carcinoma is to the epithelial cells (Lancereaux¹). Eggel, who does not recognise carcinoma with cirrhosis as a special form, found cirrhosis in about half his 163 cases of primary

¹ Lancereaux. *Gaz. méd. de Paris*, 1868, 3. s., xxiii, 646.

carcinoma. Against this view it may be urged that secondary growths are common in the liver with little or at the most only local fibrosis around them, whereas in primary carcinoma with cirrhosis the whole liver, and not merely the parts affected by the growth, is fibrotic.

(c) That cirrhosis is the primary change and that the compensatory hyperplasia of the liver cells becomes so excessive and atypical as to pass into carcinoma. The history and morbid anatomy of the cases are quite compatible with this view; the duration of the cases is much longer than in other forms of primary malignant disease of the organ; the symptoms are those of cirrhosis, and after death the cirrhosis is seen to be old and universal, while the carcinoma has the appearances of rapid growth. This view, which I have long held, is definitely stated by Turnbull and Worthington¹ who describe as successive stages, in the transition from regeneration to carcinoma in cirrhosis of the liver, (a) the regeneration nodule, (b) adenoma, (c) the carcinoma nodule.

Since it appears that cirrhosis is the primary change, and that carcinoma supervenes secondarily in much the same manner that carcinoma of the mamma follows chronic mastitis, it would, except for the objection to coining fresh names, be better not to speak of Primary Carcinoma with Cirrhosis, but to alter the title to Primary Carcinoma supervening in a cirrhotic liver, or on the analogy of Paget's disease of the nipple (dermatitis maligna), Cirrhosis Maligna, or on the analogy of carcinoma supervening on a gastric ulcer, to call it Cirrhosis Carcinomatosa.²

Morbid Anatomy.—The liver is usually little, if at all, enlarged; but in some instances it weighs twice its normal amount. There are commonly adhesions due to past perihepatitis. It is universally cirrhotic and presents multiple tumours, one of which may be so much larger that it would appear to be the primary; but Muir³ definitely states that there are multiple independent foci of growth. The nodules of growth are not umbilicated; this is because they contain but little stroma, and hence cicatricial contraction, which is at any rate an important factor in umbilication, does not occur. In an early stage the nodules are firm and white; later they degenerate, undergo necrosis, soften down, and may be yellow or green in colour. They usually project on the surface of the liver, but they may be deeply embedded in its substance. The right lobe is far the most often affected. The growth does not tend to spread by the lymphatics to the glands in the portal fissure; but is specially prone to grow into the portal and hepatic veins and thus spreads through the liver and induces secondary growths. From the portal vein the growth may extend along pervious and dilated veins in the falciform ligament. The portal obstruction induces ascites, which is a constant feature of the disease. Extension into the hepatic veins is not uncommon. In Fabian's⁴ case the inferior vena cava was obstructed. Pennato⁵ described three varieties of primary carcinoma with cirrhosis.

¹ Turnbull and Worthington. *Arch. Path. Inst. London Hosp.*, 1908, ii, 44.

² Rolleston. *Trans. Path. Soc.*, Lond., 1901, lii, 203.

³ Muir, R. *Journ. Path. and Bacteriol.*, Cambridge, 1908, xii, 299.

⁴ Fabian. *Johns Hopkins Hosp. Bull.*, Balt., 1907, xviii, 351.

⁵ Pennato. *Riforma med.*, 1897, xiii, 350.

The Curiosis of haemochromatosis

The spleen is enlarged in about half the cases.

Secondary growths are said by Hanot and Gilbert to be as frequent as in other forms of primary carcinoma of the liver. After the liver, they are most frequently seen in the lungs or on the pleura, doubtless because the growth often extends into the hepatic veins. Secondary growths may also occur on the peritoncum.

When primary carcinoma supervenes in a cirrhotic liver, the minute structure is nearly always that described by Hanot and Gilbert¹ as *Epithéliome trabéculaire*. In some instances other histological forms have been met with (cylindrical-celled, Lochlein²), but there is evidently an intimate relation between trabecular carcinoma and cirrhosis, since its histological characters are hardly ever found in other forms of primary carcinoma of the liver.

Tolot³ has recorded a case of primary trabecular carcinoma without any cirrhosis in a man aged forty-seven years who had chronic pulmonary tuberculosis of seventeen years' duration and tuberculous ostitis of the vertebrae. The hepatic condition was latent.

There are tubular columns of polyhedral or subcolumnar cells arranged in a single layer around a lumen which is usually obliterated, but may contain inspissated bile. The nuclei of the cells are situated externally, at the periphery of the tubular column. These columns branch, twist, and are separated from each other by capillaries which may contain blood. Except for the capillary walls and occasionally well-formed venules, there is no intertubular stroma. The cells shew mitotic figures, stain well, like the pseudobiliary canaliculi, and are smaller than liver cells, being intermediate in size between them and the cells of the pseudobile canaliculi. Occasionally multinuclear cells are present. Both the growths in the liver (*vide* Fig. 66) and the secondary growths in the lung have been known to shew bile-stained contents (Cloin,⁴ Ribbert,⁵ Weber⁶). Muir,⁷ however, is unable to confirm the



FIG. 63.—Section of the liver in carcinoma with cirrhosis. The growth invades the right lobe and the portal vein. (Drawn by P. L. Mummery, F.R.C.S.)

¹ Hanot et Gilbert. *Études sur les maladies du foie*, p. 41, 1888.

² Lochlein. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1907, xlii, 531.

³ Tolot. *Rev. de méd.*, Paris, 1904, xxiv, 948.

⁴ Cloin. *Prag. med. Wchnschr.*, 1901, xxvi, 261.

⁵ Ribbert. *Deutsche med. Wchnschr.*, 1909, xxxv, 1607.

⁶ Weber. *Proc. Roy. Soc. Med.*, Lond., 1910, iii (Path. Sect.), 147.

⁷ Muir, R.—*Journ. Path. and Bacteriol.*, Cambridge, 1908, xii, 299.

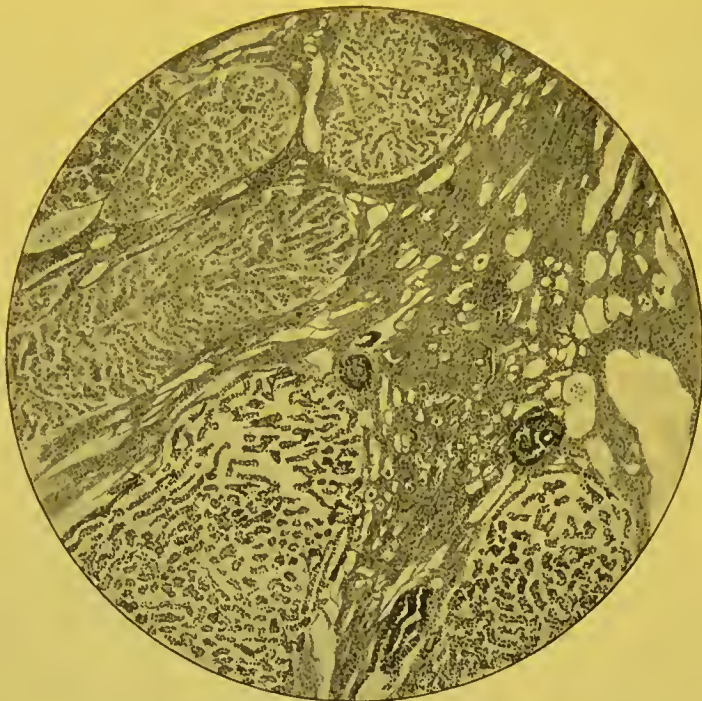


FIG. 64.—Microscopic appearances in carcinoma with cirrhosis. Cirrhosis to the left, carcinoma to the right. Under a very low power.¹



FIG. 65.—Microscopic structure of the growth under a higher power shews branching columns of subcolumnar cells separated by capillaries.

¹ For this block I am indebted to the Council of the Pathological Society of London. *Vide Transactions*, 1901, lii, 203.

and Achard and Leblanc
~~was~~ recorded earlier

Menetrier reported a case of
a liver with egophletofibrosis

Metastases occurs by the
hepatic veins. Implantation
growths may occur on the
peritoneum.

Achard ~~and~~ et Leblanc. Bull. et mém. Soc. méd. de l'hôp. de Po.
1921, 3^e sér., XLV, 1681.

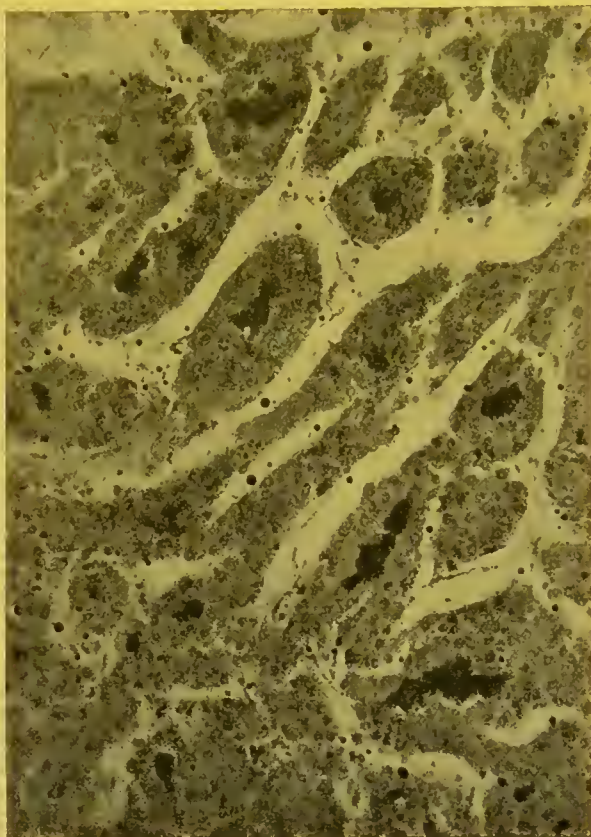
Menetrier. Bull. et mém. Soc. méd. des hôp.
de Paris, 1919, 3^e sér., XLII,
1255.

production of bile in the secondary growths. There is a wide-meshed stroma containing abundant elastic fibrils which belong to the fibrosis of the pre-existing cirrhosis (M'Connell¹). It thus differs from the stroma of other forms of primary carcinoma of the liver, which does not shew any new formation of elastic tissue (Wrench²).

This form of carcinoma is generally considered to be derived from the liver cells (Hanot and Gilbert,³ Muir). Schmieden⁴ traced the starting point of the multiple adenomas in a cirrhotic liver. In the first edition I stated my belief, which has not received any support from other writers, that the trabecular carcinoma might be a further development of the pseudobiliary canaliculi (*vide* p. 205). The development of carcinoma might be considered as an outcome of the habit of proliferation which began as a compensatory process.

When the growth is compressed or under pressure, the capillary walls may collapse and the structure of the growth is obscured. Degeneration of the cells may occur; the growth may become infiltrated with blood or invaded by fibrosis.

FIG. 66.—Photomicrograph of carcinoma with cirrhosis. Shewing tubular columns of cells enclosing masses of inspissated bile. In the capillaries separating the columns of cells a few leucocytes are seen. (Dr. H. Spitta.) $\times 220$.



6/ & cases of primary carcinoma arising in the cirrhosis due to haemochromatosis; and Kussmaul⁶ has recorded primary carcinoma in a showing cirrhosis due to schistomiasis. Loehlein⁵ collected Δ | Stewart

The clinical aspects of carcinoma with cirrhosis are practically same as those of portal cirrhosis. It is only when the liver is large nodules can be felt; as a rule, the liver is small. Ascites is const

¹ M'Connell. *Journ. Med. Research*, Boston, 1907, xvi, 13.

² Wrench. *Arch. Middlesex Hosp.*, 1905, v, 80.

³ Hanot et Gilbert. *Études sur les maladies du foie*, p. 41, 1888.

⁴ Schmieden. *Virchows Arch.*, 1900, clix, 290.

⁵ Loehlein. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1907, xlii, 591.

⁶ Kussmaul, quoted by Yamagawa. *Virchows Arch.*, 1911, cxxi, 437.

PIRIE, J. H. *Med. Journ. South Africa*, 1921, xvii, 87.

Stewart, M. J. *Brit. Med. Journ.*, 1911, ii, 11.

and may be

~~in two cases (Travis,¹ Peabody²) it was~~ markedly haemorrhagic.¹ Jaundice and pain in the hepatic region are said to be more prominent than in simple cirrhosis. Carcinoma with cirrhosis occurs, as would naturally be expected from the greater incidence of cirrhosis in men, very much more frequently in the male than in the female sex. In 49 recorded cases of which I have notes 46 were in men.

V. Primary Melanotic Carcinoma.—Three cases have been recorded as primary melanotic carcinoma of the liver. The subject is one of great pathological interest and has given rise to a good deal of discussion. In two of the cases an eye had been removed, in one for glaucoma, in the other for a melanotic sarcoma.

Hale White's³ case of primary melanotic carcinoma of the liver was in a man aged sixty-six whose eye, removed for glaucoma one year before, did not shew any sign of malignant disease. Fisher and Box's⁴ case of multiple melanotic carcinoma of the liver (which weighed 12 pounds 6 ounces), bones, lungs, and heart in a man who had had an eye removed for melanotic sarcoma fourteen years before is open to obvious criticism. Goldzieher and Bókay⁵ in 1911 described a case. Probably many would regard the growths as endo-theliomatous rather than carcinomatous.

The Origin of Primary Carcinoma.—Primary carcinoma may arise from proliferation of the liver cells, of the cubical epithelium of the small bile-ducts, or of the columnar epithelium of the intrahepatic bile-ducts. There is much difference of opinion as to the relative frequency with which primary carcinoma of the liver arises from the liver cells and from bile-duct epithelium. Eggel from a review of 163 cases concluded that the proportion was 68 per cent from the liver cells, and 32 per cent from bile-duct epithelium.⁶ (Cholangioma) } A Peperé⁶ considered the liver-cell origin 7 times commoner. Fischer⁷ believed that all carcinomas arise from the bile-ducts, even those growths with cells resembling the liver cells. Spheroidal-celled carcinoma may be derived from the liver cells or from the small bile-ducts; the larger-celled growths are probably derived from the liver cells. The trabecular form of carcinoma, seen in carcinoma with cirrhosis, is generally considered to be derived from the liver cells. Columnar-celled growths are derived from the larger intrahepatic bile-ducts or possibly from mucous glands in their walls. (hepatic)

In addition to the normal tissues of the liver it is, in accordance with Cohnheim's theory, conceivable that carcinoma might arise in pieces of other abdominal organs which have become included in the liver as the result of some irregularity in development. It has been suggested that embryonic relics of the duodenal diverticulum might persist and be the

¹ Travis, C. H. *Johns Hopkins Hosp. Bull.*, Balt., 1902, xii, 289.

² Peabody, G. L. *Trans. Assoc. Am. Phys.*, 1904, xix, 308.

³ Hale White. *Trans. Path. Soc.*, Lond., 1886, xxxvii, 272.

⁴ Fisher and Box. *Brit. Med. Journ.*, 1900, i, 639.

⁵ Goldzieher und Bókay. *Virchows Arch.*, 1911, cciii, 109.

⁶ Peperé. *I Tumori maligni primarii del fegato*, p. 171, 1902.

⁷ Fischer. *Virchows Arch.*, 1903, clxxiv, 544.

1) The blood may come from ulceration of large veins coursing over nodules of growth (Weber, Parcelier and Fromaget).
Rupture of the splenic vein has been recorded (Ogilvie)

Parcelier + Fromaget		
Mondrian		
Norwich	m	34
Lichty + Pickett	m	63
	M.	40
	M.	72
Fred.	m	64
Ogilvie	M.	31
Friedenwald	F.	52
and Fred		
Channing X	M.	55
Rosenberg	M.	57
Mallory		

There has been some discussion whether primary Carcinoma arises
uncentrically as Lownitz and Karoner believe
or multicentrically as McIndoe and Counsellor
have shown that it may do

1) the liver itself or of

2. PARCELIER et FROMAGET. Arch. de méd. expér. et d'anat. path., Par., 1912, XXIV, 180
3. Ogilvie, W.H. Guy's Hosp. Rep., 1922, LXXII, 214.

McIndoe, A.H. and Counsellor, U.S. Am. Journ. Path., Boston, 1926, II, 557

St. Zent. Museum
22108 Pyram.
Submammal Carcinoma
of Liver.

CIRIO
Starr, a hypernephroma
from the testiform lymphoid
weighing 8 1/2 lbs, and a
similarly situated tumour
of the same nature the size of a walnut
Cruickshank and
Teacher,
Fischer

Secondary growths may
show bile-formation (Mair)

Ann. Surg.
Starr, F.N.G. ~~Tumour~~ ~~Ann.~~ Surg.
1917, LXXVI, 318
Harrigan, A.H. Brit., 1918, LVIII, 395

CIRIO, L. Pathologica, Genova, 1922, XIV, 197.
Nicholson, G.W. Guy's Hosp. Rep., 1926, LXXVII, 164
CRUICKSHANK and Teacher
Journ. Path. and Bacteriol., Cambridge,
1910, XIV, 282.
Fischer. Frankfurt. Ztschr. f. Path., Wiesb.
1913, XII,

Mair. Journ. Path. and Bacteriol., Cambridge
1912, XVI,

starting-point of a carcinoma, or that a small piece of pancreas (Pepere¹) might be included in the liver. Primary malignant tumours of the liver, homologous to malignant tumours in the kidney, ^{derived} from adrenal "rests," have been described (Pepere,² Phillips and Spilsbury,³ Powell White and Mair,⁴ Hirschler⁵). But, just as the adrenal nature of the renal hypernephromas has been disputed, doubt has been thrown on the adrenal origin of these primary malignant tumours of the liver. Glynn⁶ and Nicholson⁷ believe suggests that they are really derived from the liver cells.

S/ ~~A~~ primary tumour of the liver with the structure of chorion-epithelioma ^{resembling} has been reported (Marz⁸). Brault⁸ calls these tumours angioplastie sarcoma.

Degenerative Changes in the Tumour.—The epithelial cells often shew fatty change, and necrotic changes are not uncommon; but, probably owing to rapid growth, colloid degeneration is not met with. From extensive necrosis the growth occasionally becomes cystic and some haemorrhage may take place. The fibrous tissue may undergo widespread hyaline change.

The Incidence of Secondary Growths in Primary Carcinoma of the Liver.—Secondary growths are common in the liver, and are found in other situations in more than half the cases. In Eggel's⁹ collection metastasis occurred outside the liver in 66 per cent. Secondary growths are most frequent in the immediate neighbourhood; thus, infection may spread by the lymphatics to the glands in the hilum, which are often enlarged and may press on the portal vein and bile-ducts. Lymphatic glands elsewhere, in the upper part of the abdomen and in the thorax, may be infected. Metastasis also occurs by the blood-stream; the growth may extend directly into the portal and hepatic veins, and thus give rise—(i) to fresh growths in the substance of the liver, and (ii) by embolic masses of growth which pass via the hepatic veins to secondary nodules in the lungs.

In 21 cases of primary carcinoma of the liver Lancereaux¹⁰ found growths four times in the gall-bladder, and twice each in the peritoneum, lungs, and spleen.

In a case of massive carcinoma of the liver there were innumerable secondary growths in the brain and nowhere else (Giachetti;¹¹ vide also p. 483). A secondary growth has been known to cause fracture of the femur (Goldzieher and Bókay¹²).

¹ Pepere. *Arch. per le sc. med.*, 1902, xxvi, 148.

² *Idem.* *Arch. de méd. expér. et d'anat. path.*, Paris, 1902, xiv, 763.

³ Phillips and Spilsbury. *Brit. Med. Journ.*, 1905, i, 1274; and *Trans. Clin. Soc.*, Lond., 1905, xxxviii, 179.

⁴ White (Powell) and Mair. *Journ. Path. and Bacteriol.*, Cambridge, 1907, xii, 107.

⁵ Hirschler. *Frankfurt. Ztschr. f. Path.*, 1912, ix, 343.

⁶ Glynn. *Quart. Journ. Med.*, Oxford, 1911-12, v, 157.

⁷ Marz. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1904, xxxvi, 585.

⁸ Brault. *Manuel d'histologie patholog.*, 1912, iv, part ii, 1008.

⁹ Eggel. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1901, xxx, 506.

¹⁰ Lancereaux. *Traité des maladies du foie et du pancréas*, p. 472, 1899.

¹¹ Giachetti. *Riv. di pat. nerv. e mentale*, Florence, 1907, xii, 149.

¹² Goldzieher und Bókay. *Virchows Arch.*, 1911, cciii, 75.

Extension of the primary hepatic growth into the portal or hepatic veins is much commoner in the special form of carcinoma with cirrhosis than in the other varieties of primary carcinoma. The growth in the vein may lead to very considerable dilatation of its walls, so that it is difficult to make out the exact limits of the vein in the substance of the liver.

Gilbert and Claude¹ recorded a case of extension of a massive carcinoma of the right lobe of the liver into the common bile-duct, which set up obstinate jaundice.

Incidence of Gall-stones in Primary Carcinoma of the Liver.—Although gall-stones occur in a high percentage—80–90 per cent—of cases of primary carcinoma of the gall-bladder, there is no special relation between cholelithiasis and primary carcinoma of the liver, gall-stones being merely a coincidence in malignant disease of the liver. Confusion has existed in the past, and primary carcinoma of the gall-bladder has sometimes been described as primary carcinoma of the liver, so any statistics, in which there is a high percentage of gall-stones in primary carcinoma, must be carefully criticised from this point of view.

In 41 cases of primary carcinoma of the liver examined at the Middlesex Hospital there was no case of cholelithiasis.² In 20 cases regarded as primary carcinoma of the liver, at St. George's Hospital, about two-thirds of which I saw or examined myself, 5, or 25 per cent, contained calculi in the gall-bladder.

Forms of Primary Sarcoma.—I. **Primary Massive Sarcoma.**—There is a large tumour, usually in the right lobe, which is analogous to the massive form of primary carcinoma (p. 472). There may be secondary tumours in other parts of the liver, but from their relative size there is no doubt as to the primary growth. In some instances the growth may project from the under surface of the liver so as to become pedunculated. A large proportion of the published cases of primary sarcoma appears to belong to this group. In 45 cases tabulated by Pepere,³ 22 were in this category.

The cells may be small round, spindle, or of various shapes and sizes, mixed or irregular; sometimes, especially when growth is rapid, multinuclear giant-cells are present. Haemorrhage frequently takes place into the growth and gives rise to a mottled or red appearance. The growths are often spongy on section. Large sarcomatous tumours may be very haemorrhagic and break down into cystic cavities and even imitate abscesses.

A case recorded by Bramwell and Leith⁴ simulated an abscess; aspiration was performed three times, with removal of 123 ounces of anchovy-coloured fluid.

In a woman aged sixty-four, in St. George's Hospital, there was a large cystic tumour continuous with the right lobe of the liver and reaching down to the

¹ Gilbert et Claude. *Arch. gén. de méd.*, Paris, 1895, clxxv, 513.

² Colwell. *Arch. Middlesex Hosp.*, 1905, v, 126.

³ Pepere. *I Tumori maligni primarii del fegato*, p. 118, 1902, Napoli.

⁴ Bramwell and Leith. *Lancet*, 1897, i, 170.

iliac crest. It was explored by Mr. Turner, and a large quantity of blood-stained fluid and a little growth removed; it was thought possible that it was a pancreatic cyst, but the fluid contained nothing but altered blood and had none of the characters of the fluid in a pancreatic cyst. Microscopically the growth was a mixed-celled sarcoma. At the necropsy there was an enormous cystic tumour, still containing brown, blood-stained fluid, projecting from the portal fissure and carrying the cystic and common bile-ducts and portal vein in front of it. There was, however, no jaundice or ascites. There were secondary growths in the retroperitoneal glands and in the lungs.

A woman aged fifty-nine years came under the care of Dr. Ogle in St. George's Hospital with paralysis of the left arm and leg of gradual onset, slight jaundice, ascites, a large liver and a tumour in the left hypochondrium, and oedema of the legs. Paracentesis to 20 pints was performed, and the patient

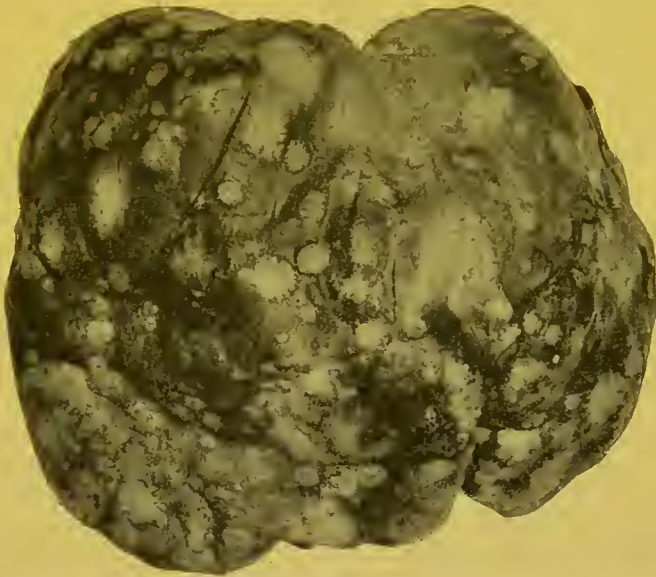


FIG. 67.—Multiple primary sarcoma of the liver shewing unbilocation. (Photographed by Dr. W. R. Harris.)

gradually got weaker and died. The liver weighed 6 pounds 10 ounces; the left lobe was completely replaced by a whitish yellow growth which in parts was of cartilaginous firmness, there were discrete secondary growths in the right lobe and massive enlargement of the portal glands. There was a secondary growth the size of a walnut in the Rolandic area of the right cerebral hemisphere. Microscopically the growth in the liver was an angiosarcoma with areas of necrosis and of extensive fibrosis.

II. Nodular, or Multiple, Primary Sarcoma.—There are a number of discrete nodules scattered in the substance of the liver which are so much of the same size that no individual nodule can be regarded as primary and antecedent to the others. This is one of the two most frequent anatomical forms of primary sarcoma. It was present in 18 out of 45 cases of primary sarcoma tabulated by Pepere. Where the nodules are small and very numerous, they tend to become confluent and to produce

either a massive growth, like the form just described, or a more diffuse infiltration, in which the cut surface has an appearance not unlike granite.

Structurally, the cells of the growth may be of very various types—spindle, round, irregular, or giant cells.

The liver of a man, aged forty-seven, who died under the care of Dr. C. Ogle in St. George's Hospital, weighed $16\frac{1}{4}$ pounds and was full of white secondary growths which were umbilicated (Fig. 67). The only other growth was in the portal lymphatic glands. It was a small spindle-celled sarcoma. There is a good example of a multiple primary spindle-celled sarcoma of the

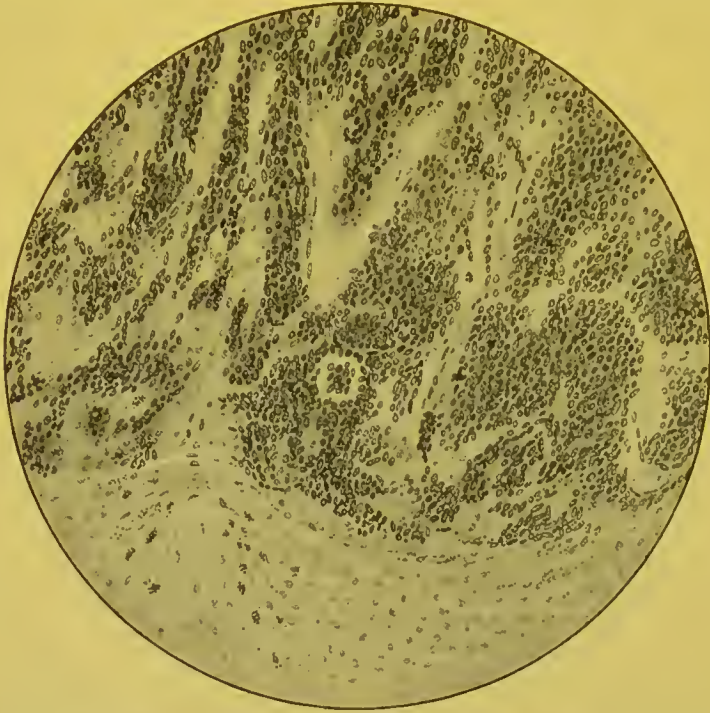


FIG. 68.—Drawing of a small spindle-celled sarcoma. The liver tissue is very lightly stained.

liver in the museum of the Royal Free Hospital. The late Miss Mabel Webb, M.B., curator of the Museum, kindly gave me a slide from this case which is reproduced above (Fig. 68).

III. Diffuse or Infiltrating Primary Sarcoma.—Sarcoma may uniformly infiltrate both lobes of the liver. This form is not infrequently seen in very early life, and must be carefully distinguished from the changes due to congenital syphilis. Some of the hard infiltrating growths, formerly spoken of as "scirrhus" of the liver, belong to this category, since they shew a structure like that of an endothelioma. There are large endothelial cells and much hyaline fibrous tissue.

IV. Primary sarcoma arising in a cirrhotic liver is very rare; in 1910 Dr. Trevor and I¹ collected 7 cases, all in males. Ascites occurred

¹ Rolleston and Trevor. *Journ. Path. and Bacteriol.*, Cambridge, 1911, xv, 247.

(Dominici and Merle; Saltykow; Jaffe)
Since then Jaffe has collected 7 more, and 3 of both sarcoma and carcinoma in a Cirrhotic liver; he concludes that therefore 29 per cent. of the known 49 primary sarcomas of the liver arise in Cirrhotic livers.

JAFFE, R. H. Arch. Int. Med., Chicago, 1924, xxxiii, 330.

Dominici ~~and~~ et Merle. Arch. ^{de med} exper. et d'anat. path., Paris, 1909, xxi, 136

Saltykow. Verhandl. d. deutsch. path. Gesellsch., 1912, xv, 272.

in 5 and was blood-stained in 3. In most of the cases the sarcoma appeared to start in the walls of the small blood-vessels; this militates against the natural assumption that the proliferation of the fibrous tissue in cirrhosis becomes so riotous as to pass into sarcoma. In Dominiei and Merle's¹ case both sarcoma and carcinoma arose in a cirrhotic liver. These 7 cases were about equally divided into round- and spindle-celled growths, and in 5 some multinucleated giant-cells were described. } ? ombr

11 V. Primary Melanotic Sarcoma of the Liver.—I have references to published cases,² but it is doubtful whether they are genuine and not secondary to a small growth in the uveal tract or in a cutaneous mole

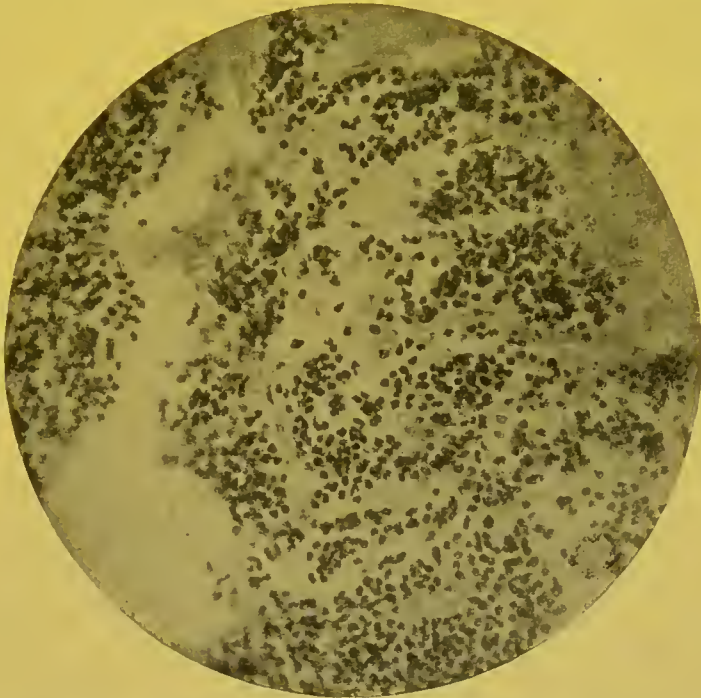


FIG. 69.—The edge of a small round-celled sarcoma infiltrating the liver diffusely in an infant. The growth was primary in the liver. (Photomicrograph by Dr. S. G. Penny.) $\times 200$.

which has been overlooked. As shewn by Dr. Pitt's case (*vide* p. 501), a very minute growth in the uveal tract, which escapes ophthalmoscopic examination and gives rise to no symptoms during life, may produce great enlargement of the liver. Thus no case can be accepted unless it is clear that the eyes were specially examined after death, and this does not appear to have been done. In the recorded cases the most that is stated about the eyes is that there were no symptoms during life.

¹ Dominiei et Merle. *Arch. de méd. expér. et d'anat. path.*, Paris, 1909, xxi, 136.

² Frerichs, *Diseases of the Liver*, ii, 326, Transl. New Sydenham Soc.; Block, O. C., *Arch. d. Heilk.*, 1875, xvi, 412; Legg, W., *St. Barth. Hosp. Rep.*, 1877, xiii, 160; Delépine, S., *Trans. Path. Soc.*, 1891, xlii, 161; Penrose, F. G., *ibid.*, 1891, xlii, 172; *Middlesex Hosp. Rep.*, 1891, p. 278; Holsti, *Brit. Med. Journ.*, 1895, i, epitome No. 395; Belin, *France méd.*, Paris, 1887; Sweet, *Brit. Med. Journ.*, 1909, ii, 1344.

Schmidt, *Tumors of the abdominal viscera*, p. 300 Amer. Transl.

HAGAR, F. R. *Surgical Clinics of Chicago*, 1919, iii, 121.

exactly
Schmidt

Origin of Primary Sarcoma.—Sarcoma may arise from the general connective tissue of the liver in the portal spaces, from the perivascular connective tissue, and from the endothelium of the blood-vessels and lymphatics. The growths arising from the tissues of the vessels, angiosarcoma, may be further divided into—(i) those arising from the lining endothelium of the blood or lymphatic vessels, the endotheliomas, and (ii) those arising from the perivascular sheaths formed of endothelium covering the vessels externally, the peritheliomas. Probably a large proportion of the primary growths usually classed as sarcoma of the liver belong to the angiosarcomas.

Among 45 cases of primary sarcoma of the liver tabulated by Pepere,¹ 22 were regarded as derived from the vessels, and of these, 11 were endotheliomas and 8 peritheliomas.

Microscopically there is a general tendency for sarcoma in the liver to assume an alveolar arrangement and so to imitate carcinoma; it is, indeed, not unlikely that some cases of large or medium-sized round-celled sarcoma of the liver have been described as carcinoma, as there is often considerable difficulty in determining the nature of the growth in such cases. One reason why a sarcoma is often alveolar is that the growth is an endothelioma, derived from the endothelium lining the small blood-vessels or lymphatics.

The forms of sarcoma met with are very various; small round-celled, large round-celled, spindle-celled, irregular-celled sarcoma with giant-cells; lymphosarcoma, angiosarcoma, including under this head the endotheliomas, and melanotic sarcoma all occur.

Condition of the Remainder of the Liver in Primary Malignant Disease.—There may, of course, be secondary growths in parts of the liver remote from the main tumour. In some cases compensatory hyperplasia of the liver cells may form nodules which are with difficulty distinguished from secondary growths. The liver cells in the neighbourhood of the growth may contain haemosiderin. Local venous engorgement from pressure on the trunks of the intrahepatic veins, or local bile-staining from compression of the bile-ducts, may also be met with. The occurrence of cirrhosis has already been dealt with. As a curiosity, the association of primary malignant disease of the liver² with hydatid cysts in the organ may be mentioned (*vide* p. 397).

Growths in the liver may be invaded by micro-organisms; this may occur during life and give rise to suppuration. It is not uncommon for micro-organisms to gain access to the growth at or after death; they are then of no importance. Hebb³ found long bacilli in a case of primary carcinoma, and Delépine⁴ staphylococci in a melanotic sarcoma of the liver.

¹ Pepere. *I Tumori maligni primarii del fegato*, 1902, p. 118.

² *St. Thomas's Hosp. Rep.*, 1900, xxix, 141; Loehlein, *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1907, xlii, 531.

³ Hebb, R. G. *Westminster Hosp. Rep.*, 1888, iii, 180.

⁴ Delépine, S. *Trans. Path. Soc.*, 1890, xlii, 161.

SECONDARY MALIGNANT TUMOURS OF THE LIVER

Incidence.—*Numerical Ratio between the Incidence of Secondary and Primary Malignant Tumours of the Liver.*—Secondary malignant growths in the liver are very common, while primary growths of the liver are rare. The ratio between primary and secondary malignant disease of the liver is often stated to be about 1 to 20. Even this is rather overstating the frequency of primary malignant disease of the liver. Possibly cases of malignant disease of the gall-bladder or larger bile-ducts have been regarded as primary in the liver by some observers and so have tended to vitiate statistics.

Hale White¹ puts the proportion of undoubted primary to secondary carcinoma as 1 to 21. He found that primary malignant disease was the cause of death in 0·1 per cent, and that secondary growths were present in 3·47 per cent of patients examined after death at Guy's Hospital. Hanseemann,² in twenty years—1870–1889—found that 258 necropsies shewing malignant disease in the liver had been performed in the Pathological Institute at Berlin; of these, either 6 or 4 were primary in the liver; this shews a ratio of primary to secondary growths of nearly 1 to 40.

Incidence of Secondary Carcinoma and Sarcoma in the Liver.—Secondary carcinoma is far more often met with than secondary sarcoma.

In 100 cases of secondary malignant disease of the liver abstracted from the post-mortem records of St. George's Hospital, 77 were carcinoma and 23 sarcoma. The cases of sarcoma include endothelioma, such as the malignant tumours of the suprarenal, of which there were 5. There were 3 cases of melanotic sarcoma. In Hale White's figures the percentage was 91·4 carcinomatous, and 8·6 sarcomatous, secondary growths. In his 361 cases of secondary growths in the liver at least 330 were carcinomatous.

The smaller incidence of secondary sarcoma in the liver is readily explained not only by the greater frequency of carcinoma, but also by the infrequency of primary sarcoma in the alimentary canal, or, in other words, within the territory of the portal vein. Sarcoma, like pyaemia, travels by the veins to and through the lungs, which filter out the micro-organisms or infecting cells and thus at their own expense protect the rest of the body.

Sex.—Secondary malignant disease of the liver is rather more frequent in women than in men.

During the years 19¹³~~14~~¹⁰–19¹³~~14~~¹⁰ there were, according to the Registrar-General's returns for England and Wales, ~~21,138~~^{24,021} female and ~~14,139~~^{15,823} male deaths from malignant disease of the liver; though these figures include malignant disease of the gall-bladder, which is much commoner in women, it is probable that they represent very fairly the sex-incidence of secondary malignant disease. Hale White estimated the ratio as 4 to 3.

¹ Hale White. *System of Medicine* (Allbutt and Rolleston), 1908, iv, part i, 204.

² Hanseemann. *Berlin. klin. Wchnschr.*, 1890, xxvii, 353.

The greater frequency of secondary malignant disease of the liver in women depends not only on the greater incidence of malignant disease in that sex, but also on the special predominance of malignant disease of the mamma and female genital organs. Secondary growths in the liver often follow cancer of the mamma and genital organs, but rarely occur in malignant disease of lip, mouth, and tongue, which are much commoner in the male than in the female sex.

The incidence of cancer generally, and especially of the alimentary canal, is absolutely and steadily increasing (Payne¹). According to the Registrar-General's statistics, although at the present time women suffer more severely from malignant disease than men in the aggregate, the incidence of malignant disease has increased more rapidly among men than in the other sex. It is, therefore, highly probable that secondary malignant disease of the liver is becoming more frequent in males than formerly.

In 100 cases of secondary malignant disease of the liver examined at St. George's Hospital and taken in continuity from the post-mortem records, 1892–1902, I was surprised to find that the number of males (66) was nearly double that (34) of the females. In 144 cases at Guy's Hospital 77 were in men and 67 in women (Weaver²).

Age.—Secondary malignant disease of the liver occurs most frequently after forty years of age.

The average age of 100 cases of secondary malignant disease of the liver examined at St. George's Hospital was 49·8 years. The average ages of the 66 males was 51·3 years, and of the 34 females, 47 years.

The average age is, as might be expected, higher in the cases of secondary carcinoma than in those of secondary sarcoma.

Among 100 cases of secondary malignant disease of the liver the average age of 77 cases of carcinoma was 51·9 years (50 male cases, average age, 53·1 years; 27 female cases, average age, 48·5); while the average age of 23 cases of secondary sarcoma was 43 years (16 males, 43·8 years; 7 females, 41·1).

Probably the earliest recorded case of secondary carcinoma of the liver is Zuppinger's³ in a girl aged twelve years. The primary growth was a columnar-celled carcinoma of the sigmoid flexure. Ruczynski⁴ reported a similar case in a boy aged thirteen years, the primary growth being in the splenic flexure.

Morbid Anatomy.—The liver is sometimes of the normal size, with a few secondary growths scattered over its surface. Often, however, the secondary growths in the liver increase very rapidly, and if the primary growth in the alimentary canal is comparatively stationary, the liver may reach a very large size; in such cases it often weighs 16 pounds. The

¹ Payne, J. F. *Lancet*, 1899, ii, 765.

² Weaver. *Guy's Hosp. Rep.*, 1909, lxiii, 225.

³ Zuppinger. *Wien. klin. Wchnschr.*, 1900, xiii, 389.

⁴ Ruczynski. *Prag. med. Wchnschr.*, 1904, xxix, 531.

Cosens report carcinoma of the stomach
with hepatic metastases in a boy
aged 19

Cosens, W B. Brit. med. Journ., 1917, i, 649

vascularity of the liver, the presence of glycogen, and the high temperature provide conditions specially favourable to rapid tumour growth. In cases, such as carcinoma of the breast or melanotic sarcoma of the uveal tract, in which the primary growth may have been removed after infection of the liver has actually taken place, the liver may subsequently become greatly enlarged. The largest livers known occur in secondary malignant disease. Osler¹ mentions a liver weighing $30\frac{1}{2}$ pounds, and Christian² one of $33\frac{1}{3}$ pounds. Richard Powell³ refers to a liver weighing nearly 40 pounds but does not state the cause of enlargement.

Secondary invasion of the liver is hardly ever limited to a single nodule of growth. The liver may contain multiple and discrete growths, or may be diffusely infiltrated for a greater or less extent, as is sometimes well seen in carcinoma of the breast and in melanotic sarcoma. When widely infiltrated, the liver is enlarged, but preserves its general shape and anatomical outlines very fairly.

"Farre's tubercles" was formerly a well-known synonym for secondary growths in the liver. This writer described "*Tubera circumscripta*" and "*Tubera diffusa*," corresponding to the two forms mentioned above.⁴

In some instances nodules originally separate may unite into a large irregular mass. The growths are scattered throughout the liver, but are especially frequent near the surface of the organ, and are rarely seen on section when entirely absent from the surface. They grow rapidly and receive their blood-supply from the hepatic artery, which is sometimes considerably enlarged.

In this connexion it is interesting to refer to a plate of Bright's⁵ shewing a large artery supplying a mass of secondary new-growth.

Whether carcinomatous or sarcomatous, the naked-eye appearances of the nodules have much in common. The peritoneum is often thickened and opaque over the nodules. They are usually white in colour, and are not infrequently bile-stained and may be speckled with blood or extremely haemorrhagic. In secondary melanotic sarcoma there may be isolated pigmented nodules, areas of diffuse melanotic infiltration, or both combined. In some cases the secondary melanotic growths are almost or quite devoid of pigment, at any rate to the naked eye. Sarcomatous growths are more likely to be haemorrhagic and to soften into pseudocysts; as a rule, they are not depressed in the centre or umbilicated, a change often seen in secondary carcinomatous growths on the surface of the liver. The statement that secondary sarcomatous nodules are never umbilicated, and may thus be distinguished from secondary carcinomatous growths in the liver, is too dogmatic and must admit of some exceptions.

¹ Osler. *Principles and Practice of Medicine*, p. 568, ed. vi, 1905.

² Christian, H. A. *Am. Med.*, Phila., 1903, v, 131.

³ Powell, R. *Observations on Bile and its Diseases, and on the Economy of the Liver*, p. 17, 1800.

⁴ Farre, J. R. *Morbid Anatomy of the Liver*, 1815, London.

⁵ Bright. *Guy's Hosp. Rep.*, 1836, i, 638.

In St. Bartholomew's Hospital Museum there is the liver of a boy, aged ten years, enormously enlarged and studded with umbilicated nodules secondary to sarcoma of the kidney (No. 2215 c).

The dead-white colour of some secondary carcinomatous nodules, especially columnar-celled growths, may give rise to an appearance very like a gumma, so that considerable difficulty may arise in distinguishing between the two conditions, especially when only a limited examination can be made, as at exploratory laparotomies.

I have several times examined fragments removed during life which have turned out to be columnar-celled growths secondary to a latent carcinoma in the stomach or colon, and which it was naturally hoped might be gummatous. Gouget¹ described a columnar-celled carcinoma of the liver which was at first regarded as a gumma (*vide* p. 353).

The consistency of the growths varies considerably. Diffuse areas of infiltration may be hard, but as a general rule the larger the size of a secondary growth, the softer it is, since degeneration and necrotic changes are more prone to supervene than in smaller nodules. Small discrete nodules cut with the same kind of resistance as a cream cheese.

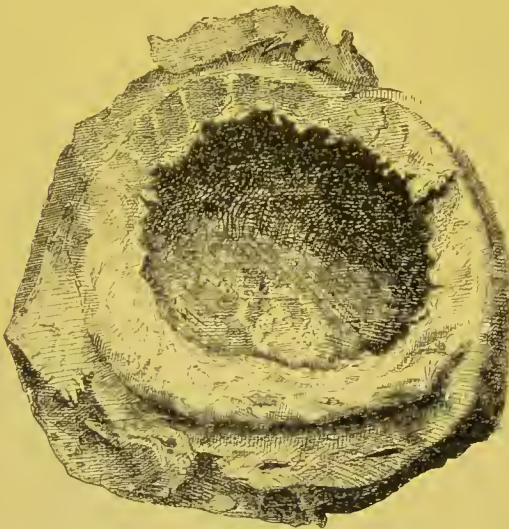


FIG. 70.—Cyst due to softening of a secondary carcinomatous growth in the liver, from a specimen in St. George's Hospital Museum. (Series ix, 184 L.) (Drawn by L. Jones, M.S.)

Degenerative Changes.—The central parts of the larger nodules readily undergo fatty degeneration and necrosis, and may have a caseous or softened appearance. The necrosed tissue readily undergoes autolysis or self-digestion by intracellular enzymes (proteases) of the dead cells. A rapidly growing mass of carcinoma may present the honeycombed and

softened appearance of actinomycosis. Extreme softening may in some instances be due to suppuration from infection. The necrosed portions may be yellow or green from bile-staining, or may become infiltrated with blood. This haemorrhagic condition is more often seen in sarcoma, but it may also occur in secondary carcinomatous growths. Sometimes the haemorrhage into the degenerated growth is so profuse as to lead to serious syncope, but when this occurs, the growth has usually ~~ruptured~~ ~~and allowed blood to pass~~ into the peritoneal cavity. In other instances

Leaked |

1. a |

¹ Gouget. *Bull. Soc. Anat.*, Paris, 1890, lxxv, 605.

which may then resemble chorion-epithelioma (RISEL, Stewart

RISEL. BEITR. z. path. Anat. u. z. allg. Path., JENA, 1907, XLII, 233.

Stewart. Journ Path. and Bacteriol., Cambridge, 1913, XVII, 409

a sanguineous ascitic effusion is due to comparatively insignificant leakage from a small nodule.

Colloid degeneration in a secondary growth in the liver is rare.

There is a mass of colloid carcinoma, the size of a man's fist, in St. Bartholomew's Hospital Museum, secondary to a growth in the rectum (No. 2216 H).

According to Schueppel,¹ diffuse colloid cancer of the peritoneum may spread by the lymphatics of the capsule of the liver and pass into its substance like strings. Eventually a whole lobe of the liver may become transformed into a colloid mass.

Myxomatous and hyaline degeneration may attack the fibrous tissue of a slow-growing secondary nodule of carcinoma, or occur in secondary endotheliomatous nodules even though growing rapidly.

Formation of Pseudo-cysts.—Degeneration and softening of secondary malignant growths may lead to the formation of cystic cavities. This may occur in any form of carcinoma, even in the squamous-celled variety, and in sarcoma. It is, however, rather rare.

In a case of carcinoma of the stomach recorded by Hawthorne² there were numerous cysts in the right lobe of the liver, due to softened new-growth; the largest had a diameter of $4\frac{1}{2}$ inches. Aspiration during life resulted in the withdrawal of 58 ounces of blood-stained fluid. The case imitated an abscess. In a case of carcinoma of the pylorus recorded by Nicaise³ the liver (75 ounces) contained numerous secondary growths, and had a tongue-shaped lobe with a haemorrhagic cyst due to destruction of the growth. In a case of carcinoma of the cardiac end of the stomach in a woman in St. George's Hospital in 1909, secondary growths in the liver contained clear alkaline fluid. In a case of carcinoma of the liver, probably secondary to the pancreas, in a man aged fifty-one, there were numerous cystic spaces with caseous contents. Microscopically the growth was a carcinoma, shewing a transition from a columnar to a spheroidal type, with considerable fibrosis and extensive necrotic and cystic changes. The liver is in the Museum of the Royal Free Hospital. Voelcker⁴ described secondary squamous-celled carcinomatous nodules with cystic change, a smooth thin layer of new growth alone being left as the wall of the cyst. In a similar case the cyst wall could easily be peeled out of the liver; it closely resembled a hydatid cyst and contained clear yellow fluid (Thomson⁵). There is a somewhat similar specimen with cysts the size of a tangerine orange in St. Bartholomew's Hospital Museum secondary to a growth in the oesophagus. In a case described by Sharkey⁶ the liver was studded with cysts lined by squamous epithelium.

In St. Bartholomew's Hospital Museum there is a specimen (2215 E) of secondary sarcomatous growths which have broken down so extensively that the appearance is not unlike that of cystic disease of the liver in the adult; the primary growth was in the skin of the back. I have seen the same thing in a

¹ Schueppel. v. Ziemssen's *Cyclopaedia of Practical Medicine*, ix, 338. English transl., 1880.

² Hawthorne, C. O. *Clin. Journ.*, Lond., 1896, viii, 361.

³ Nicaise, V. *Bull. Soc. Anat.*, Paris, 1900, 6. s., ii, 146.

⁴ Voelcker, A. F. *Trans. Path. Soc.*, Lond., 1896, xlvii, 43.

⁵ Thomson, H. C. *Practitioner*, 1899, lxii, 411.

⁶ Sharkey, S. J. *Trans. Path. Soc.*, Lond., 1884, xxxv, 374.

secondary endothelioma of the liver which weighed 18 pounds, the primary growth being in the left kidney (*vide* p. 523). Von Horsch¹ describes extensive cystic changes in hepatic metastases secondary to sarcoma of the stomach.

Umbilication.—Not uncommonly secondary growths on the surface of the liver shew a central depression or umbilication. It occurs in comparatively slow-growing carcinomatous nodules and is very rare in secondary sarcoma (*vide* p. 489). According to Géraudel² it does not occur in secondary nodules due to lymphatic invasion from the surface of the liver.

This umbilication is due to the cells in the central part of the nodule undergoing degeneration and becoming compressed by the surrounding fibrous tissue, which, from the greater age of the growth in the centre, is better developed than in the more recent peripheral parts of the nodule. Another factor is the more exuberant cellular proliferation at the edge of the nodule, which leads to a heaping-up of growth. The depression of the oldest part of an oyster's shell, viz. that near the hinge, illustrates the production of umbilication (Wilks³). Umbilication is often absent in rapidly growing nodules of small size.

Effects of Secondary Growths.—Secondary growths on the surface of the liver frequently set up perihepatitis and so give rise to pain. It is very rare for a secondary growth on the surface of the liver to grow directly into the abdominal wall; this is probably prevented by the respiratory movements. It does, however, sometimes occur, and the diaphragm or anterior abdominal wall may be so firmly united by the growth to the liver that after death they can be separated only by the knife. A growth on the anterior surface of the liver may infect the opposed surface of the parietal peritoneum without any adhesions between the two, the growth being implanted by contact.

Growths in the liver frequently press on the branches of the portal vein and may thus help to cause ascites; pressure on the hepatic veins is often seen, and gives rise to local chronic venous engorgement. In a certain number of instances the secondary growths project into the veins and set up thrombosis; detachment of small pieces of growth projecting into the lumen of the hepatic veins leads to metastatic growths in the lungs. Occasionally a secondary growth may form a polypoid mass in the hepatic or portal veins.

Pressure on the intrahepatic bile-ducts is common and results in local bile-staining of the liver tissue. In rare instances malignant disease in the liver, after eating its way into the larger bile-ducts, may grow along the lumen of the duct without infiltrating the wall of the tube (Fauvel, Durand-Fardel,⁴ Gilbert and Claude⁵). This process is like the downward projection of a renal growth into the ureter.

¹ v. Horsch. *Deutsche Ztschr. f. Chir.*, Leipz., 1907, xc, 98.

² Géraudel. *Arch. de méd. expér. et d'anat. path.*, Paris, 1910, xxii, 363.

³ Wilks. *Pathological Anatomy*, p. 474, 1889.

⁴ Fauvel, Durand-Fardel. Quoted by Devic et Gallavardin, *Rev. de méd.*, Paris, 1901, xxi, 570.

⁵ Gilbert et Claude. *Arch. gén. de méd.*, Paris, 1895, clxxv, 513.

Histology.—Structurally the secondary nodules resemble the primary growth. When secondary to carcinoma of the stomach, the hepatic growths may be either columnar-celled or spheroidal-celled; when the colon is affected, the hepatic growths are columnar-celled; in both these instances, however, the secondary tumours may differ somewhat from the primary, the cells shewing a transition from the columnar to the spheroidal type. When secondary to carcinoma of the breast, the growth is spheroidal-celled; and when a primary growth in the lower part of the oesophagus infects the liver, the structure of the secondary nodules is that of a squamous-celled carcinoma. But here again from more rapid growth the cells may be spheroidal rather than squamous.

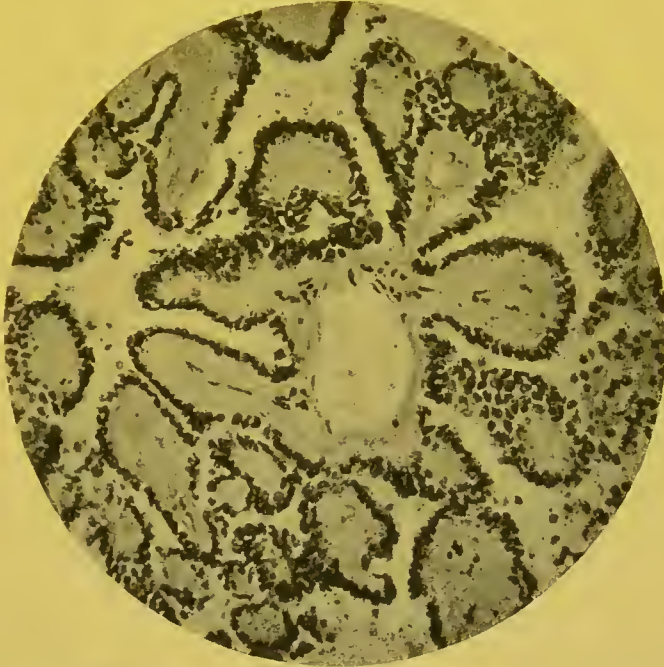


FIG. 71.—A secondary perithelioma of the liver. The primary growth was in the kidney (*vide* case on p. 526). (Photomicrograph by Dr. H. Spitta.)

Secondary sarcoma is very often alveolar in its arrangement; this depends on the growth starting from emboli inside the small vessels of the liver.

In some cases of secondary carcinoma the cells of the liver, which are atrophied and compressed by the invading cells, are considerably pigmented. This may be due to retained bile-pigment. In cases in which the liver is independently pigmented, as in malaria or in haemochromatosis, a secondary growth in the liver is not pigmented.

A man aged forty-six died under my care with a primary endothelioma in the spine. The liver was of a deep brick-red colour and had a number of minute white nodules in it, which are shewn in Fig. 72 to be quite free from pigment.

In some instances of secondary carcinoma there is proliferation of the liver cells in parts remote from the growth, which may be regarded as an attempt to replace the destroyed liver substance—a compensatory hyperplasia.

In a case of secondary sarcoma Cornil¹ observed proliferation of the hepatic cells and the formation of pseudobile canaliculi at a short distance from the growth (compare p. 496).

Brault² noticed that in some instances in which the cells of the secondary growths contain glycogen the hepatic cells contain none.

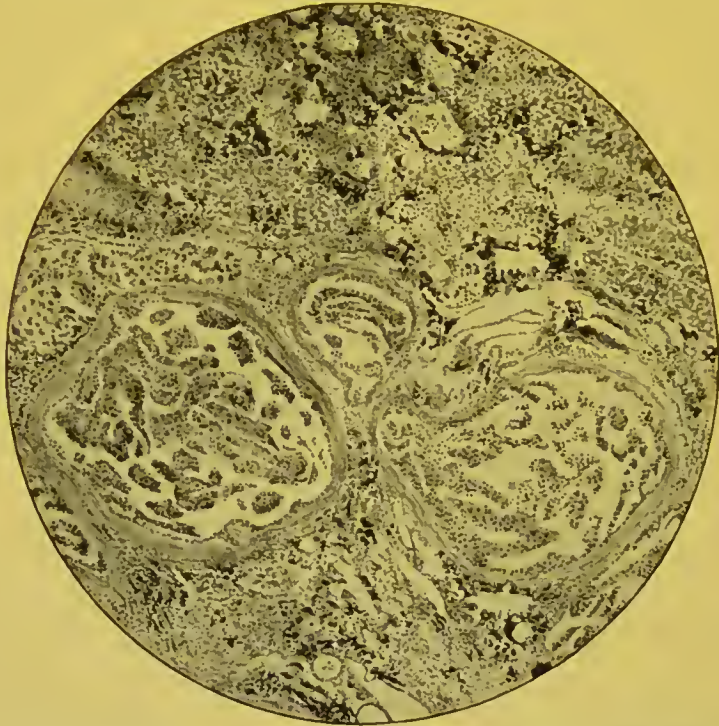


FIG. 72.—Liver with secondary endotheliomatous growths. The liver is pigmented from haemochromatosis; the small nodules of growth, entirely free from pigment, are mainly surrounded by remains of the fibrous tissue of the portal spaces. The primary growth was in the spine. $\times 28$.

A certain amount of local fibrosis is common around carcinomatous nodules in the liver; this may be regarded as an attempt on the part of the organ to limit the extension of the growth. When this change is more general and there is obstinate jaundice, the fibrosis has been thought to be due to biliary obstruction set up by the tumour.³

Condition of the Remainder of the Liver.—From pressure on the bile-ducts the whole or parts of the liver may be bile-stained. The occurrence of local areas of chronic venous engorgement from pressure

1. a) ¹ Cornil. *Bull. Soc. Anat.*, Paris, 1902, lxxvii, 195.

² Brault. *Arch. de méd. expér. et d'anat. path.*, Paris, 1902, xiv, 467.

³ Gilbert et Claude. *Arch. gén. de méd.*, Paris, 1895, clxxv, 513.

on branches of the hepatic veins has just been referred to. In some instances the engorgement is so extreme that extravasation occurs in the immediate neighbourhood of nodules of growth and produces an appearance of a haemorrhagic infarct. Infarctions, both haemorrhagic and anaemic, have been met with in the liver, as a result of venous obstruction due to pressure, exerted by nodules of growth, on the portal or hepatic veins (*vide* p. 104).

Secondary malignant growths are very rare in cirrhotic livers; they occur, of course, in the special form of primary carcinoma with cirrhosis.

In 608 cases of secondary malignant disease of the liver the organ was cirrhotic in two (Colwell¹). Hale White² mentions a case of a man with sarcoma of many bones with a growth in a cirrhotic liver. Poulain³ met with a secondary nodule in a cirrhotic liver; the primary growth was a columnar-celled carcinoma of the stomach. Achard and Laubry⁴ described secondary growths in a large cirrhotic liver, the primary growth being in the colon.

It is not very common to find cirrhosis of the liver in patients with intra-abdominal malignant disease; this is, of course, the main reason for the rarity of secondary growths in cirrhotic livers. It is conceivable that portal obstruction interferes with the passage of emboli of infecting cells from the colon and stomach, and that the cirrhotic liver is not a good soil for their development.

When, as not uncommonly happens, secondary growths occur in tight-laced livers, the constriction lobe attached to the right lobe may be quite free from growth, suggesting that its somewhat isolated position has prevented the advent of emboli of infecting cells by the blood-stream. On the other hand, secondary growths may be almost confined to the constriction lobe, as if its diminished resistance was specially favourable to the development of any embolic masses of new growth which gain access to it. Examples of these two different events are given in the section on the tight-laced liver (p. 9).

As a coincidence there may be secondary growths in a liver containing hydatids. I have met with one such case (*vide* p. 397), and Dr. R. N. Salaman has shown me two specimens in which secondary nodules of carcinoma were in contact with old hydatid cysts. References to other recorded cases are given on p. 397. Secondary growths may arise in a syphilitic liver, and even in one containing gummas, but it is a rare coincidence.

A man aged forty who died with carcinoma of the colon had gummas in one testis and much scarring of the liver, which contained numerous gummas and nodules of new growth. The man was in St. George's Hospital in 1891. I did the necropsy and microscopically determined that there were both gummas and new growth in the liver.

¹ Colwell. *Arch. Middlesex Hosp.*, 1905, v, 135.

² Hale White. *Allbutt's System of Medicine*, 1897, iv, 208.

b.c. ³ Poulain. *Bull. Soc. Anat.*, Paris, 1899, 6. s., i, 1089.

⁴ Achard et Laubry. *Bull. et mém. Soc. méd. des hôp. de Paris*, 1902, 3. s., xix, 335.

Tuberculosis and secondary growths may exist in the same liver. There is no antagonism between the two processes, as was formerly thought.

Dalton¹ recorded a case of secondary columnar-celled carcinoma in the liver with miliary tubercles in the immediate neighbourhood. The primary growth was in the sigmoid flexure.

In very rare instances ordinary secondary growths, due to an extra-hepatic neoplasm, are associated with a primary carcinoma of the intra-hepatic bile-ducts.



FIG. 73.—A liver shewing the constriction lobe divided and its halves separated so as to display large secondary carcinomatous growths in its substance. There were in addition two small white nodules only in the right lobe of the liver. The primary growth was carcinoma of the breast. (Drawn by L. Jones, M.S.)

In Necker's² case a cirrhotic liver contained two hydatid cysts, secondary spindle-celled sarcoma, and a primary carcinoma derived from the bile-ducts. In a secondary melanotic sarcoma of the liver primary carcinomatous nodules, derived from the bile-ducts and ascribed to the irritation of the secondary melanotic growths, have been described (Taylor and Teacher³).

The existence of two different kinds of secondary growths in the same liver must be excessively rare.

Simon⁴ records the case of a woman who died, two years after removal of her right eye, with widespread melanotic sarcoma. The liver was greatly enlarged

¹ Dalton. *Trans. Path. Soc.*, Lond., 1885, xxxvi, 235.

² Necker. *Ztschr. f. Heilk.*, Wien u. Leipz., 1905, xxvi (*Abt. path. Anat.*), 351.

³ Taylor and Teacher. *Journ. Path. and Bacteriol.*, Cambridge, 1908, xii, 441 ; 1910 xiv, 205.

⁴ Simon. *Bull. Soc. Anat.*, Paris, 1900, xxiv, 213.

with melanotic sarcoma and contained a white nodule which microscopically had the structure of columnar-celled carcinoma. Unfortunately the stomach and intestines were not examined at the necropsy, so the site of the primary growth was not discovered.

Methods of Metastasis.—The dissemination of secondary growths is mainly due to embolism of the intrahepatic blood-vessels. In most cases, since the primary growth is within the territory drained by the portal vein, the emboli of carcinomatous cells travel up that vessel. When the primary growth is in the eye and in other distant parts of the

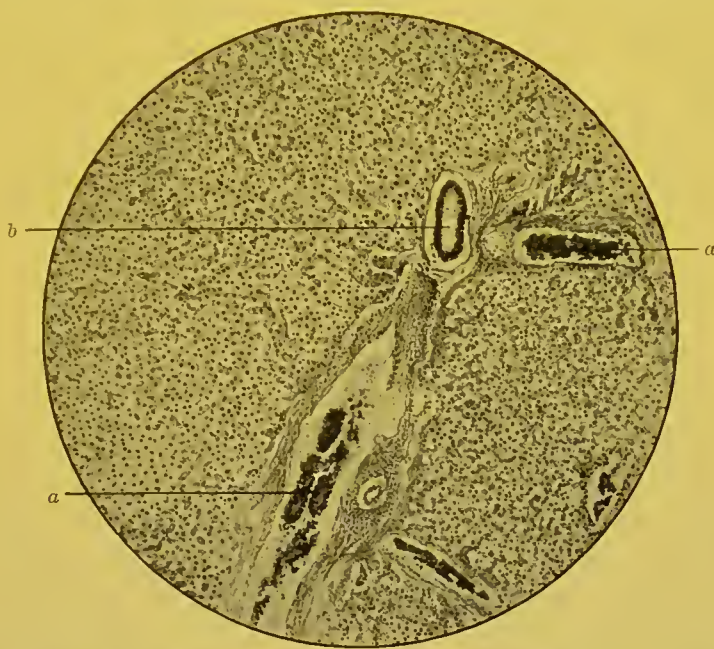


FIG. 74.—Minute emboli in the intrahepatic branches of the portal vein (*a*). A small bile-duct is represented at *b*. From a case of secondary carcinoma of the liver. The primary growth was in the stomach. $\times 50$.

body, the emboli are distributed by the hepatic artery. It appears from Handley's¹ investigations that mammary carcinoma spreads by the lymphatics to the liver ("epigastrie invasion"), and that the usual statement that it is embolic is erroneous. Primary carcinoma of the mamma may extend by the lymphatics to the linea alba and round ligament into the liver. With the exception of primary carcinoma of the mamma and probably of the oesophagus the dissemination of secondary growths in the liver, unlike the spread of carcinoma elsewhere, is not by way of the lymphatic vessels.

This depends on two factors: (i) That the liver does not receive the lymphatics of the other abdominal viscera, but sends its own out at the portal fissure; hence carcinoma would have to spread in against the direction of the flow of lymph. This does occur, but it is quite excep-

¹ Handley. *Lancet*, Lond., 1905, i, 1047.

tional. In carcinoma of the stomach growth can sometimes be seen tracking into the portal fissure. Colloid cancer of the peritoneum may pass into the subserous lymphatics of the capsule and invade the liver. (ii) That the primary carcinomatous growths in the alimentary canal frequently invade the radicles of the portal vein. When this has occurred, emboli readily pass up to the liver, inasmuch as there are no valves in the portal vein.

Secondary Growths due to Retrograde Embolism.—In rare instances a carcinomatous or sarcomatous embolus, when in the right auricle or inferior vena cava close to the diaphragm, is driven, by some expiratory effort, into the hepatic veins against the stream of blood. Thus Welch¹ refers to Heller's cases of malignant disease of the caecum in which a loose plug of growth was found in one hepatic vein, and to Bonome's case of cancer of the thyroid gland with metastatic growths in the liver developing from plugs in the hepatic veins. My friend Professor Adami has told me of a primary growth of an accessory adrenal which extended into the inferior vena cava and right auricle, where it ended in a ball-like termination and gave rise to secondary growths, evidently by retrograde embolism, in the liver.

Direct Invasion of the Liver by a Growth.—It is not very uncommon for a growth starting in the gall-bladder to infiltrate the liver by direct continuity, and in some instances the appearances have led to an erroneous diagnosis of primary malignant disease of the liver. Primary carcinoma of the extrahepatic bile-ducts may extend up into the liver.

Malignant disease of the stomach, especially at the cardiac end, may spread directly into the liver. In Fenwick's² 131 cases of gastric carcinoma this occurred in 13·7 per cent. In such cases the growth in the liver may undergo necrosis or become infected and give rise to a gangrenous abscess cavity and to fever. In rare instances carcinoma of the lower end of the oesophagus may extend directly into the liver. I have seen direct invasion of the liver occur in cases of primary endothelioma of the right suprarenal.

Situation of the Primary Growth in Secondary Malignant Disease of the Liver.—The most frequent sites of the primary carcinomatous growths are in the alimentary canal, viz. stomach, colon, oesophagus, pancreas, from which small emboli of infecting cells pass along the portal vein and form carcinomatous emboli in the capillaries of the liver; thus, secondary growths start and are for a time inside the hepatic capillaries, whereas primary carcinoma is outside the vessels, or extra-vascular.

In 100 consecutive cases of secondary malignant disease of liver abstracted from the post-mortem books of St. George's Hospital from 1892–1902 the following were the situations of the primary growths :

¹ Welch. *Allbutt's System of Medicine*, 1899, vi, 232.

² Fenwick. *Cancer and other Tumours of the Stomach*, p. 55, 1902.

<i>Carcinoma.</i>		<i>Sarcoma.</i>	
Stomach	24	Suprarenals	5
Colon	12	Mediastinum	4
Oesophagus	10	Melanotic	3
Pancreas	8	Generalised	3
Gall-bladder	5	Bone	2
Uterus	4	Lung	2
Mamma	3	Stomach	1
Kidneys	3	Liver	1
Bile-ducts	3	Thyroid	1
Biliary papilla . . .	1	Uterus	1
Vermiform appendix .	1		—
Bladder	1		23
Ovary	1		
Generalised	1		
<hr/>			
77			

The *stomach* is the most frequent site of the primary growth in secondary malignant disease of the liver, about 25 per cent of the cases of secondary malignant disease of the liver are secondary to malignant disease of the stomach.

In malignant disease of the stomach there are secondary growths in the liver in about 35 per cent of the cases (Fenwick¹). Welch gives 30 per cent, Perry and Shaw² 40 per cent, and Lebert 40·9 per cent. In 228 cases of primary carcinoma of the stomach examined after death at St. George's Hospital there were secondary growths in the liver in 71, or 31 per cent (Packer³); Colwell⁴ found 86 metastases in 227 cases, or 37 per cent. In 47 fatal cases of gastric carcinoma tabulated by Osler and McCrae⁵ the liver was affected in 23. According to Fenwick, the right lobe is involved in carcinoma of the pylorus and middle of the stomach and the left lobe when the cardiac end is the site of carcinoma.

Carcinoma of the colon is probably, after malignant disease of the stomach, the most frequent cause of secondary growths in the liver.

In 100 cases of secondary malignant disease of the liver the colon or rectum was the site of the primary growth in 12. In 100 fatal cases of primary carcinoma of the colon examined after death I found secondary growths in the liver in 34. But in many of these the secondary nodules were quite small and could not have given rise to any clinical manifestations. Of these 100 cases, 52 were males (19 secondary growths) and 48 females (15 secondary growths).

It is remarkable that secondary growths in the liver are more frequent and often more extensive when the primary growth in the colon is small than when it is large.

In a case mentioned by Weber⁶ the liver weighed 27½ lbs., whilst the primary growth in the rectum was the size of a large cherry.

¹ Fenwick. *Cancer and other Tumours of the Stomach*, p. 182, 1902.

² Perry and Shaw. *Guy's Hosp. Rep.*, 1904, lviii, 155.

³ Packer. *Med. Chronicle*, Manchester, 1907, xlii, 213.

⁴ Colwell. *Arch. Middlesex Hosp.*, 1896, vii, 157.

⁵ Osler and McCrae. *Cancer of the Stomach*, p. 141, 1900.

⁶ Weber, F. P. *Proc. Roy. Soc. Med.*, Lond., 1910, iii (Path. Sect.), 150.

A patient may be quite unconscious of a growth in the rectum when the liver is greatly enlarged. Hence the rectum should always be examined in suspected malignant disease of the liver when the site of the primary growth is not clear.

Metastatic growths in the liver are found in about half the cases of *primary carcinoma of the gall-bladder*.

In Musser's ¹ 100 cases the liver contained secondary nodules in 52 and was directly invaded by the growth in 2 more.

Secondary growths are frequently found in the liver in fatal cases of *carcinoma of the breast*. Thus in 423 necropsies of mammary carcinoma tabulated by Gross ² the liver was affected in 206, or 48·6 per cent; in 460 cases of carcinoma of the mamma examined after death at the Middlesex Hospital there were metastases in the liver in 215, or 46·7 per cent (Colwell ³); in 735 cases investigated by S. Paget ⁴ the liver was involved in 241, or 34 per cent. This lower estimate is much the same as Beadles' ⁵ observation that in 100 cases of malignant disease of various parts of the body secondary growths in the liver were found in 36. In 422 cases of mammary carcinoma, tabulated by Handley, ⁶ the liver was affected in 90, or 21·3 per cent.

Carcinoma of the oesophagus is more likely to lead to metastases in the liver when the lower third of the gullet is the site of the growth.

In 85 cases of oesophageal carcinoma examined after death at St. George's Hospital there were secondary nodules in the liver in 17 instances; and in 28 out of 91 at the Middlesex Hospital; or a percentage of 25 in the 176 cases. In rare instances the oesophageal growth is so small as to be entirely latent while the liver is greatly enlarged.

Carcinoma of the uterus rarely gives rise to secondary growths in the liver; among 818 cases at the Middlesex Hospital there were 97 with hepatic metastases, or 12 per cent.

Secondary Sarcoma.—As already pointed out, secondary sarcoma is much less frequent in the liver than secondary carcinoma, (*vide* p. 487). Hale White found 8·6 per cent of the cases of secondary malignant growths in the liver to be sarcoma. My figures, which give a much higher percentage of secondary sarcoma, viz. 23, include cases of endothelioma, for example, malignant growths primary in the suprarenals.

~~Melanotic Sarcoma~~.—The occurrence of secondary melanotic growths in the liver is well known, and is so striking that once seen—and all museums contain specimens—it is never forgotten. Since this is a matter

¹ Musser. *Boston Med. and Surg. Journ.*, 1889, cxxi.

² Gross. *Am. Journ. Med. Sc.*, Phila., 1888, xc, 235.

³ Colwell. *Arch. Middlesex Hosp.*, 1905, v, 123.

⁴ Paget, S. *Lancet*, Lond., 1889, i, 571.

⁵ Beadles, C. F. *Trans. Path. Soc.*, Lond., 1896, xlvii, 77.

⁶ Handley. *Lancet*, Lond., 1905, i, 1048.

occurred in 15 out of 17 necropsies collected by Chaliier and ~~an~~ Bonnet who, however, erroneously include Heaton's case among the fifteen. Churchman refers to 67 cases with hepatic metastases in 87 per cent.

ChALIER et Bonnet. Rev. de chir., Par., 1913, XLVII, 78.
Churchman Am. Journ. Med. Sci., Phila., 1918, CLV, 63.

of common knowledge, it might be thought that it is common in ordinary hospital work. This, however, is not the case.

In twelve years—1890–1901—3806 necropsies were performed at St. George's Hospital, and in 3 cases there were secondary melanotic growths in the liver, or in 0·08 per cent.

The primary sites of malignant melanomas are chiefly those where the pigment melanin is present, namely, in the uveal tract and in the skin, especially in pigmented moles. It may be mentioned that melanotic cutaneous growths, though from custom usually spoken of as sarcomas, are now generally regarded as pigmented endotheliomas. In rare instances a primary melanoma has been seen in the rectum or at the margin of the anus; ~~but secondary growths in the liver are very rare in these cases.~~

~~De Back and Vanderlinden¹ described a case with secondary growths in the liver. In neither Heaton's² case nor in one examined by myself were there hepatic metastases.~~

Recurrence in the liver usually occurs within three years of the appearance of the primary growth, and the prognosis is very bad. Occasionally long periods of immunity are met with. In one of the first published cases of secondary melanotic sarcoma there was an interval of eight or nine years between the removal of the eye and the occurrence of symptoms indicating hepatic growth.³

In Lilley's⁴ case ten years elapsed between excision of an eye for melanotic sarcoma and death with growths in the liver. Lawbaugh⁵ recorded a case in which seventeen years elapsed between enucleation of the eye for a melanotic sarcoma and death from the same growth in the liver. The most extraordinary case is one in which there were thirty-two years between the removal of the eye for melanotic sarcoma and death from the same disease in the liver. Wilder,⁶ who mentions this case, saw the liver in Kundrat's laboratory at Vienna.

Very occasionally the liver may be widely infiltrated with secondary melanotic sarcoma, while the primary growth is very small and may escape notice.

The London Hospital Museum⁷ contains a liver infiltrated with melanotic sarcoma and weighing 16 pounds; the primary growth in the eye was only discovered at the necropsy. Dr. Newton Pitt kindly shewed me a similar case. A man aged twenty-nine had cutaneous tumours, one of which was excised and found to be an alveolar melanotic sarcoma, and enlargement of the liver. Ophthalmoscopic examination of the eyes was negative. There was no melanin

¹ ~~De Back et Vanderlinden. *Belgique méd.*, Nov. 9, 1899.~~

² Heaton. *Trans. Path. Soc.*, Lond., 1894, xlv, 85.

³ Murchison. *Ibid.*, 1873, xxiv, 123.

⁴ Lilley. *Lancet*, Lond., 1911, ii, 363.

⁵ Lawbaugh. *Journ. Amer. Med. Assoc.*, 1900, xxxv, 1363.

⁶ Wilder. *Ibid.*

⁷ Vide *London Hosp. Gaz.*, 1900, vii, *Clin. Supplement*, p. 1.

in the urine. At the necropsy there was widespread generalisation of the growth; the liver weighed 16 pounds. There was a small growth in the outer edge of the uveal tract in the right eye.

Lawford's and Collins' statistics as to the results of melanotic sarcoma of the uveal tract shew that in 26 cases known to have died there was evidence that the liver was affected in 16.

In age-incidence malignant melanotic growths resemble carcinoma and rarely occur in early life.

In 103 cases of sarcoma of the uveal tract, all of which, except one, about which no note was made, being more or less melanotic, collected by Lawford and Collins,¹ the average age was 48·4 years, the extremes being 15 years and 84 years. In 35 cases of secondary melanotic growths in the liver which I collected, the average age was 48·7 years, or 46·7 years for the males and 53·3 for the females, the extremes being 27 years and 75 years.

Of Lawford's and Collins' 103 cases, 59 were males and 44 were females; in my 35 collected cases in which the sex was stated, 25 were males and 10 were females; this shews a greater preponderance of males than in the series of primary growths of the uveal tract. The right eye was affected 41 times and the left 60 times in Lawford's and Collins' cases, while in my cases of hepatic growths the right eye was rather more frequently the primary seat of growth, but the numbers are small.

Metastatic melanotic tumours of the liver are more often secondary to a primary growth in the uveal tract than in the skin. Thus, in 37 cases of melanotic sarcoma in the liver the primary growth was 24 times in the eye and 13 times in the skin. The growths in the liver following cutaneous melanosis are not so big or so striking as those secondary to melanotic sarcoma of the uveal tract. Primary cutaneous melanoma may, indeed, cause widespread metastases, the liver being one of the few organs not affected. In a case² in which the growth began in a left toe there were numerous growths in the skin elsewhere, the lungs, kidneys, and brain, but the liver and spleen were quite free. In most of my collected cases in which the liver contained growths secondary to cutaneous melanosis, the organ was little above the ordinary size, though in 2 cases it weighed over 7 pounds; on the other hand, some of the largest livers recorded have been secondary to melanotic sarcoma originating in the eye. Thus, Litten³ reported a liver weighing 27 pounds, Sayre⁴ one of 23 pounds, and Hamburger⁵ one of 22 pounds. I have examined 2 cases in which the weight was within a few ounces of 16 pounds. The average weight of the liver in 22 cases of melanotic growth secondary to a growth in the uveal tract was 13 pounds 3 ounces. This difference in the

1. a) ¹ Lawford and Collins. *Roy. London Ophth. Hosp. Rep.*, 1893, xiii, 104, 395.
² Lévi. *Bull. Soc. Anat.*, Paris, 1899, lxxiv, 709.
³ Litten. *Deutsche med. Wchnschr.*, 1889, xv, 41.
⁴ Sayre. *Trans. New York Path. Soc.*, 1879, iii, 42.
⁵ Hamburger. *Johns Hopkins Hosp. Bull.*, 1898, ix, 50.



liability to metastasis in the liver exhibited by melanotic sarcoma starting in the skin and in the eye is shewn in the two following cases :

Primary Growth in the Skin of the Big Toe ; Widespread Metastasis.—A man aged sixty-four years had had his foot removed for a melanotic sarcoma starting in the big toe after an injury. The growth recurred in the stump, and at the necropsy, which I performed, there were metastases in the lungs, brain, left kidney, pancreas, abdominal glands, and liver. The liver contained numerous isolated growths, but weighed only 52 ounces. The growth was a spindle-celled sarcoma.

Primary Growth in the Eye, Excision, Recurrence in the Liver.—A man aged fifty-nine years was admitted under my care with the history that his right eye had been removed two years previously for a melanotic sarcoma. The liver was enormously enlarged and knobby, but there was no ascites. He had melanuria. The legs were oedematous. At the necropsy there were a few small secondary growths on the diaphragm, in the mucous membrane of the intestine, and in one adrenal. The liver was enormously enlarged, weighing 15 pounds 12 ounces, and was extensively occupied by growths of a spindle-celled melanotic sarcoma.¹

The liver is a favourite site for secondary infiltration in melanotic sarcoma of the uveal tract. In a few cases it coexists with an intra-ocular growth, but it usually occurs within three years after removal of the eye and generally without there being any local recurrence in the optic nerve or orbit. It would thus appear that the infective cells of the growth must remain latent in the liver for some time. The liver may be the only organ in the body affected, or almost every viscus and tissue may shew metastases. It is remarkable that the cells of melanotic sarcoma being, as they usually are, larger than the cells of the other sarcomas which are stopped by the lungs, manage to pass through the pulmonary capillaries and to infect the liver. The liver evidently offers the most favourable situation for the growth of melanotic sarcoma.

The growths in the liver almost always progress very rapidly, but in Litten's² case there was evidence of a tumour in the liver for the exceptionally long period of four years.

The liver may be either nodular, from the presence of discrete growths, or diffusely infiltrated, so that the organ, though enlarged, is not altered in shape. When thus infiltrated, the liver substance presents a variegated appearance like that of granite, exceptionally it is so extensively infiltrated that it looks as if it had been soaked in tar. Not uncommonly the liver shews nodules in some parts and diffuse infiltration in others. As a rare event a pedunculated growth may be found attached to the liver. Sometimes parts of the growths are free from pigment and pale ; in other cases the pigment is sparse and the tumours, to the naked eye, appear of a mottled grey or greenish colour. Perihepatitis is not common.

Histologically, secondary melanotic growths in the liver may be

¹ Rolleston. *Lancet*, Lond., 1899, i, 1273.

² Litten. *Deutsche med. Wchnschr.*, 1889, xv, 41.

sarcomatous or endotheliomatous; when sarcomatous, they may be spindle-celled, oval or oat-shaped, or round-celled. The cells start as emboli inside the hepatic capillaries, and hence the growth frequently has a more or less alveolar appearance.

Malignant Disease Primary in the Suprarenals.—In 26 cases of primary malignant disease (carcinoma, endothelioma, or sarcoma) of the adrenals collected by Marks and myself¹ the liver was the organ most frequently affected by secondary growths, namely, in 14, and was, in addition, invaded by direct continuity in 3. In 46 cases of sarcoma of the suprarenals collected by Pepper² there were metastases in the liver in 14. A suprarenal growth may extend into the inferior vena cava and give rise to retrograde embolism in the hepatic veins and so to secondary growths, as in Adami's case (p. 498).

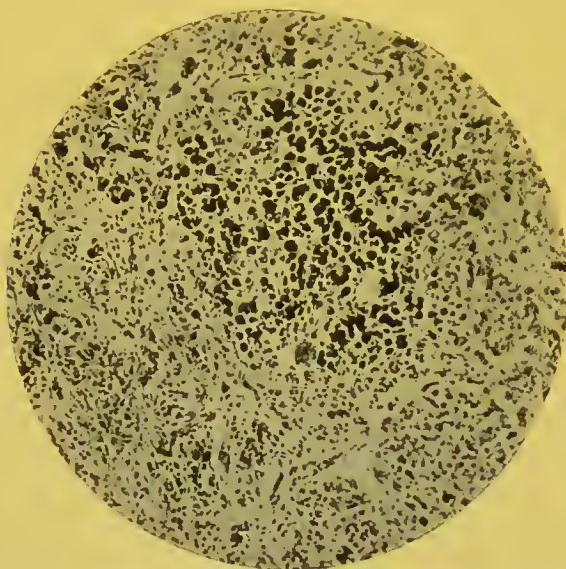


FIG. 75.—Secondary infiltration of the liver with a melanotic sarcoma. The cells are chiefly round-cells, and vary considerably in the amount of melanin they contain. The arrangement is more or less alveolar. The primary growth was in the uveal tract. (Photomicrograph by Dr. S. G. Penny.)

In generalised sarcoma the liver often contains discrete nodules of growth. The portal spaces may be infiltrated with green growth

in chloroma, which has been regarded in the past as a round-celled sarcoma, but is a form of acute lymphocytic leukaemia. Trevithick³ has reported a case of this kind.

An exceptional origin for secondary growths in the liver is so interesting that a brief reference may be made to it. Embryomas and teratomas in the abdominal cavity may become malignant and infect the liver.

Out of 10 cases of malignant teratoma collected by Montgomery,⁴ 4 led to secondary growths in the liver. A non-malignant implantation-growth on the surface of the liver has followed rupture of an ovarian embryoma (Hulke,⁵ Latham⁶). Abdominal dermoids (embryomas) are practically teratomas, as they are not composed of skin alone, but of tissues derived from all three layers of the embryo, and are really, as Wilms⁷ shewed, complex tumours.

¹ Rolleston and Marks. *Am. Journ. Med. Sc.*, Phila., 1898, cxvi, 390.

² Pepper. *Ibid.*, 1901, cxxi, 287.

³ Trevithick. *Lancet*, Lond., 1903, ii, 158.

⁴ Montgomery. *Journ. Exper. Med.*, N.Y., 1898, iii, 259.

⁵ Hulke. *Trans. Path. Soc.*, Lond., 1873, xxiv, 157.

⁶ Latham, A. *Ibid.*, 1899, 1, 232.

⁷ Wilms. *Deutsche Arch. f. klin. Med.*, Leipz., 1895, lv, 289.

Malignant Chorion-epithelioma may give rise to secondary haemorrhagic secondary growths in the liver; Weber refers to a case in a man with death from rupture of the hepatic metastasis.

F. P. Weber. Practitioner, London, 1918, CI, 31.

CLINICAL FEATURES OF MALIGNANT TUMOURS OF THE LIVER

It will be most convenient to describe the signs and symptoms of primary and secondary malignant tumours of the liver together, since the two conditions are so frequently indistinguishable, and to note the points of difference between them in a special section (*vide* p. 526). The latency of malignant tumours of the liver is dealt with on p. 519.

Physical Signs.—The facial aspect of a patient with advanced malignant disease of the liver is that of a grave and wasting illness. The eyes are usually sunken, and the skin dirty, sallow, or shewing varying degrees of jaundice. But in the earlier stages, even when nodular enlargement of the liver can be felt, there may be little to note in the patient's aspect except some anaemia, and it cannot be maintained that the facial aspect is characteristic at this early stage. Steady loss of flesh and weight are very common in malignant disease of the liver. The subcutaneous fat is absorbed, and as a result the cheeks and temples fall in and give the patient a hollow and haggard appearance. Absorption of fat helps to render the skin inelastic. During the emaciation an associated fatty tumour has greatly diminished in size (Bell¹).

The patients may actually gain in weight as the liver increases in size.

A boy, aged fifteen years, with primary carcinoma of the liver, gained $19\frac{3}{4}$ pounds before his death; this was due to the enormous liver, which weighed nearly 16 pounds, or two-fifteenths of the total body weight, and also to ascites (Acland and Dudgeon²). A man who died in St. George's Hospital, under the care of Dr. C. Ogle, from multiple primary sarcoma of the liver, gained 7 pounds in the last three weeks of life. At the necropsy the liver weighed $16\frac{1}{4}$ pounds, and there was about one pint of ascitic fluid (*vide* Fig. 67).

The gain in weight of the individual as a whole, if not due to ascites and oedema, depends on the increase in the tumour growth more than counterbalancing the loss due to general emaciation. The same phenomenon is sometimes seen in rapidly growing renal sarcomas in infants. Some increase in weight and improvement in general nutrition may follow careful feeding, especially in the early stages of malignant disease of the liver.

Progressive emaciation is more marked in secondary malignant disease of the liver, for here there is in addition the effect of the primary growth, often in the stomach or colon, which has already, and perhaps for some considerable time, interfered with digestion and assimilation of food. In such cases nutrition may be so impaired that bed-sores develop; their occurrence is probably favoured by the fact that the patient generally lies in one position—on the back.

¹ Bell. *Brit. Med. Journ.*, 1902, i, 1588.

² Acland and Dudgeon. *Lancet*, Lond., 1902, ii, 1310.

Exceptionally, however, death may occur from secondary malignant disease of the liver when the patient is well nourished or even fat.

A man aged sixty-three years, a patient in St. George's Hospital, had enlargement of the liver and ascites. He had never had haematemesis and was not jaundiced. He was thought to have cirrhosis. At the necropsy, the abdominal walls, mesentery, etc., contained much fat. There was a primary carcinoma of the hepatic flexure, and the liver ($10\frac{1}{2}$ lbs.) was full of secondary growths.

In primary malignant disease the progress of the disease is so rapid, death often following even within three months of the first symptoms, that there may not be time for emaciation and there may be plenty of subcutaneous fat.

In a very rapid case which I examined after death some years ago the man—who was sent into the hospital for intestinal obstruction—was very fat. An enormously fat woman aged forty, weighing over 20 stone, died with multiple growths in the liver, which weighed 10 pounds 11 ounces. Except for a few minute nodules in the spleen, no other growth could be found elsewhere in the body. It was apparently a case of multiple primary carcinoma of the liver. Microscopically the growth was a rapidly growing carcinoma composed of cells shewing transitional forms from columnar to spheroidal type.

Cachexia is important in differentiating malignant from other enlargements of the liver, such as deeply seated hydatid cysts, hypertrophic biliary cirrhosis, and from some cases of nutmeg liver. The *progressive* character of the cachexia is of especial importance. The causation of cachexia is probably to be found in an auto-intoxication emanating from the rapidly proliferating epithelial growths. As is well known, the cells of many normal glands, such as the pancreas, thyroid, suprarenal, provide an internal secretion which passes directly into the lymphatics or veins, and helps to keep up the condition of equilibrium we know as health. When epithelial cells run riot and form atypical growths, or what might be called abnormal glands, it is not unreasonable to believe that they may produce a morbid internal secretion which, when absorbed, poisons the body generally, and gives rise to the cachexia of malignant disease. In support of this view it is noticeable that innocent tumours composed of normal tissues do not, however large they may be, give rise to cachexia, unless they mechanically interfere with absorption and nutrition. There are other ways in which poisonous substances can be supplied by malignant growths. As the result of necrosis and autolysis of growths, toxic bodies are probably produced which, when absorbed, will tend to produce toxæmia and cachexia.

Fever.—There has been a general impression that malignant disease of the liver is not accompanied by fever or only by transient elevations of temperature due to independent causes. This, however, is very far from being a rigid rule; Eggel¹ estimated that fever was present in 14 per cent of 147 collected cases of primary carcinoma of the liver, and

¹ Eggel. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1901, xxx, 506.

Russell¹ found some degree of pyrexia in nearly two-thirds of a small collection of various forms of malignant disease of the liver. Thus, fever may occur in malignant disease of the liver, whether primary or secondary, and its presence does not necessarily exclude new growth in favour of some form of hepatic suppuration. Fever in malignant disease of the liver may be divided into two categories: (i) Uncomplicated cases. The raised temperature may be due to the rapid growth and multiplication of cells inside the liver; cases occur in which no other cause is forthcoming; this may be seen in primary malignant disease of the liver. It is particularly likely to occur in rapidly growing sarcoma in young persons. The temperature, which rarely rises above 102° F., may continue for weeks. The liver forms a very suitable soil for rapid tumour growth and hence fever is more frequent in malignant disease of the liver than of other organs. As pointed out by Butlin and Colby,² fever is not very uncommon in cases of sarcoma of the femur and tibia. (ii) Complicated cases. Fever may be due to the absorption of poisons or micro-organisms from the ulcerated surface of the primary growth in the stomach, colon, or elsewhere. Again, the necrotic growths may become infected with micro-organisms either from the alimentary canal or from the blood-stream, and thus fever and rigors may result. Suppuration is occasionally associated with secondary growths in the liver. In some instances a primary growth in the stomach may directly invade the liver and carry infection into that organ (*vide* p. 121).

A woman aged fifty-four had a primary spheroidal-celled carcinoma of the cardiac end of the stomach, which perforated directly into the under surface of the liver and produced a large abscess in close contact with numerous secondary nodules in the liver. The hepatic abscess leaked into the peritoneal cavity and set up fatal peritonitis.

Suppurative cholangitis may supervene in the course of malignant disease of the liver when the ducts are dilated from obstruction; this is more likely to occur in secondary malignant disease of the liver, since obstruction to the ducts is comparatively infrequent in primary growths of the liver substance.

Osler³ refers to a case of cancer of the liver in which intermittent fever and rigors were so marked that the question of abscess was raised. After death, in addition to secondary growths, there were several abscesses caused by the growths compressing the bile-ducts.

A good example was seen in a woman aged forty-four who had jaundice due to growths in the portal fissure, secondary to carcinoma of the splenic flexure of the colon, compressing the hepatic ducts. The intrahepatic bile-ducts shewed suppuration. There was high fever in this case, which was under the care of my colleague, Sir Isambard Owen.

¹ Russell, J. W. *Brit. Med. Journ.*, 1907, i, 312.

² Butlin and Colby. *St. Barth. Hosp. Rep.*, 1895, xxxi, 31.

³ Osler. *Johns Hopkins Hosp. Rep.*, Balt., 1891, ii, 1.

Primary carcinoma of the second part of the duodenum involving the biliary papilla (perivaterian duodenal carcinoma) is especially prone to set up suppurative cholangitis; usually it kills the patient in this way before there has been time for secondary growths to occur in the liver, but secondary growths may be found in association with suppurative cholangitis.

A man aged fifty-two was under the care of my colleague, Sir Isambard Owen, with jaundice, rigors, and a lump in the prostate. The necropsy revealed a primary columnar-celled carcinoma of the biliary papilla, secondary growths in the liver, suppurative cholangitis, empyema of the gall-bladder, and pyaemic abscesses in the prostate and kidneys.

Malignant disease and cirrhosis of the liver may both be accompanied



FIG. 76.—Primary multiple sarcoma of liver (*vide* fig. 67 on p. 483). The lower margin of the liver is marked on the skin. Cachexia is pronounced. The subcutaneous veins are enlarged. (Photograph by Dr. F. Golla.)

by fever. Cases of malignant disease of the liver with fever may simulate pyelephlebitis, hepatic abscess, or even enteric fever (Guthrie¹).

The *abdomen* may be greatly distended by the enlarged liver, the outline of which may even be visible, the skin is often tense, and enlarged veins, usually from obstruction of the inferior vena cava, may be visible.

The *liver* is enlarged; the enlargement is progressive, and may be so extreme that the organ eventually occupies most of the abdomen; it moves with respiration, and after death may not come down so low as in life, being drawn up by the last expiration. When the surface of the organ is irregular, the growth is in the great majority of cases secondary; the nodules may be felt to be umbilicated or depressed in the centre, and

¹ Guthrie. *Clin. Journ.*, Lond., 1908, xxxiii, 144.

The spleen is very rarely enlarged in malignant disease of the liver unless there is portal thrombosis which is specially likely to occur in primary carcinoma in a cirrhotic liver. In rare cases of widespread round-celled infiltration (diffuse lymphocytoma) of the liver and spleen, the resemblance to leukaemia is very close until the blood is examined; in some of these cases the meninges are invaded and nervous symptoms occur (Mosny and Mouton). Secondary growths in the spleen are rare. Microscopic infiltration (Kettle) of the spleen may account for some cases of splenomegaly. I have seen a spleen weighing two pounds & easily palpable during life which showed congestion only. I have ~~also~~ seen splenomegaly both in Sarcoma & Carcinoma of the liver. Care must be taken not to regard the enlarged left lobe as the spleen.

Mosny et Mouton. Arch. de méd. exp. et d'anat. path., Par., 1913, xxv, 194

Kettle. Journ. Path. and Bacteriol., Camb., 1912-13, xvii, 40

thus can be distinguished from the hobnails of a cirrhotic liver, from which the progressive character of the enlargement further separates it. Sometimes, however, the depressions between hobnails on a cirrhotic liver convey the impression of umbilication, and umbilication cannot always be felt over secondary hepatic growths. In cirrhosis the enlargement is more uniform than in malignant disease which chiefly affects the right lobe.

In primary malignant disease of the liver there is usually a uniform, firm, and hard tumour in the position of the right lobe of the liver, and occasionally there are, in addition, nodules of secondary growth elsewhere on the surface of the liver. This condition cannot be distinguished from secondary malignant disease in which the primary growth is latent. Occasionally the growth is so soft that it fluctuates and imitates an abscess (*vide* p. 522). In rare cases it may pulsate, either because the growth is a haemorrhagic sarcoma or from transmitted pulsation.

Sir Lauder Brunton¹ met with a case of malignant disease of the left lobe of the liver with pulsation and a bruit over the tumour which imitated an abdominal aneurysm.

A mass of new growth may be found at the umbilicus in association with secondary malignant disease of the liver. Small outlying secondary growths may also form in the falciform ligament of the liver, and be felt during life near the linea alba; their presence greatly assists in forming a diagnosis of malignant disease. They may, however, be closely simulated by small islands of fat left intact when emaciation is rapid.

In a case of secondary malignant disease of the liver in which small masses were felt during life in the line of the falciform ligament I could not find after death the growths ~~which I thought I had~~ felt during life, ~~and~~ which had assisted in the diagnosis.

Nodules of new growth on the surface of the liver may be closely simulated by perihepatic adhesions or by irregularities due to gummas and syphilitic cicatrices.

A *venous hum* or murmur is occasionally heard over the liver. It may be due to an excessively vascular or haemorrhagic growth, to pressure, exerted by nodules of growth or enlarged glands, on the portal vein, or possibly to constriction of the inferior vena cava where it is in contact with the liver. *Friction* from perihepatitis, set up by growths in the capsule, may be detected in some instances and is usually accompanied by pain and tenderness on pressure. It is commoner in secondary than in primary growths of the liver, not only because secondary growths are met with in such an overwhelming proportion, but because they are more likely to invade the capsule than primary growths.

Haemorrhages into the skin, mucous membranes, and other parts of the body may occur in association with jaundice and cholaemia. They may

¹ Lauder Brunton. *Trans. Med. Soc. Lond.*, 1896, xix, 117.

also be met with when there is little or no jaundice, though the liver is extensively infiltrated by growth, and when rapidly destructive changes in the liver cells are in progress, which interfere with the formation of fibrinogen. Exceptionally a haemorrhagic tendency is manifest in an early stage of malignant disease of the liver and then passes away. As the result of failure in the antitoxic function of the liver cells, poisons absorbed from the intestinal tract pass into the general circulation and give rise to cholaemia. The presence of bile in the circulation is quite subordinate in importance to these toxic substances.

Jaundice and *ascites* are not essential, but rather accidental, symptoms. They may be due to a growth pressing on the portal vein and bile-duct, ~~or on their main branches~~; a secondary growth in the glands in the portal fissure may thus give rise to both. One or both of them may appear at almost any period of the disease. They are not evidences of the extent or severity of the disease, but only of its situation. They both occur in about 50 per cent of the cases.

Jaundice, if marked, is a severe complication, and by giving rise to cholaemia may accelerate the necessarily fatal issue. In 41 cases of primary malignant disease of the liver jaundice was present to some degree in 23, or 56 per cent (Colwell¹); Eggel² found it in 61 per cent. Jaundice when present is usually comparatively slight and not of the marked character and prolonged duration sometimes seen in secondary malignant disease of the organ. Jaundice may depend on associated catarrh of the bile-ducts, and may then be relieved by treatment (Mayo Robson³), but during life it is generally explained by mechanical pressure. The onset of jaundice in malignant disease may be sudden and accompanied by sickness and vomiting, so as to simulate catarrhal jaundice very closely, but instead of disappearing, it persists and becomes deeper (*vide* p. 665).

In secondary malignant disease of the liver jaundice is rather more likely to supervene and to occur early when the primary growth is near the bile-ducts, for example, at the pylorus or in the gall-bladder. Primary growths in these positions are prone to spread directly to the portal fissure and to produce obstructive jaundice, whereas multiple embolic growths scattered over the periphery of the liver have much less tendency to induce biliary obstruction.

A man aged thirty-four years became jaundiced a few weeks before his death from primary spheroidal-celled carcinoma near the pylorus. The lesser omentum was $\frac{3}{4}$ inch thick from infiltration with growth which surrounded and compressed the common bile-duct. Microscopically the bile-duct was invaded by growth, the infiltration extending up to the neck of the gall-bladder and into the portal fissure. The gall-bladder and intrahepatic bile-ducts were distended, but the extrahepatic ducts were all compressed. The liver weighed

¹ Colwell. *Arch. Middlesex Hosp.*, 1905, v, 128.

² Eggel. *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1901, xxx, 506.

³ Mayo Robson. *Brit. Med. Journ.*, 1897, i, 641.

Experimental ligation of some but not of all, the bile ducts does not cause jaundice (Harley and Barrett), even when $19/20$ of the liver substance is obstructed (McMaster and Rous). In man jaundice may be associated with obstruction of some only of the bile ducts, but it is then probably due to some general lesion of the liver area, the ducts or to hemolysis.

66 ounces and had a green, nutmeggy appearance ; there were small masses of growth in the intrahepatic branches of the portal vein. This patient was in St. George's Hospital.

Obstruction to one of the intrahepatic bile-ducts may give rise to jaundice ; in such a case the other bile-ducts convey bile into the intestine and the faeces are not clay-coloured. At the necropsy of such cases pressure on the gall-bladder will cause bile to flow into the duodenum.

A man aged fifty-five years, a barman, was admitted to St. George's Hospital with a large liver and distinctly palpable glands above the right clavicle. The liver was manifestly knobby, but no umbilication could be made out. The urine contained much urobilin ; the faeces contained bile, and jaundice of no great intensity finally developed. Except for some difficulty in swallowing, there was nothing to suggest the site of the primary growth. At the necropsy the liver (14 lbs.) contained numerous secondary growths, some of which were umbilicated. Pressure on the gall-bladder brought bile out of the duodenal papilla. There were numerous growths in the liver near the portal fissure, which compressed some of the bile-ducts. No calculi ; no cirrhosis of the liver, which was somewhat nutmeggy. ~~The spleen showed venous engorgement.~~ There was a primary spheroidal-celled carcinoma in the middle third of the oesophagus, and a secondary growth, probably due to implantation but resembling to the naked eye another primary neoplasm, at the cardiac end of the oesophagus. There were a few ounces only of ascitic fluid.

On the other hand, experimental ligature of the left hepatic duct in cats performed by V. Harley and Barratt¹ did not cause jaundice. Possibly this was due to some collateral biliary anastomoses between the right and left lobes of the liver.

An interesting, but extremely rare, cause for jaundice is extension of malignant disease along the lumen of the bile-ducts in an analogous manner to the prolongation of a renal growth down the ureter. This has been known to occur in both primary and secondary malignant disease of the liver.

Gilbert and Claude² recorded primary carcinoma of the liver in a girl aged twenty-two, in whom attacks of biliary colic and obstinate jaundice were due to a process of the growth extending in a polypoid form into and blocking up the common bile-duct.

When jaundice is absent, the skin is usually anaemic, sallow, and sometimes dirty-looking ; slight pigmentation, as in other forms of abdominal disease, is sometimes seen.

Legg³ figures marked pigmentation suggesting argyria in a man with melanotic growths in a liver weighing 5700 grams (200 oz.) who also had melanuria. Williamson⁴ lays stress on small black patches in the skin as diagnostic of internal melanotic growth.

¹ Harley and Barratt. *Brit. Med. Journ.*, 1898, ii, 1743.

² Gilbert et Claude. *Arch. gén. de méd.*, Paris, 1895, clxxv, 513.

³ Legg. *Trans. Path. Soc.*, Lond., 1884, xxxv, 367.

⁴ Williamson, R. T. *Lancet*, Lond., 1900, ii, 1874.

Ascites.—When the liver is extensively infiltrated with new growth its capillaries become obstructed over a correspondingly wide area, either by pressure from without, as in primary carcinoma, or from the presence of growth inside their lumen, as in secondary growth, and especially in one form of primary angiosarcoma (endothelioma), and in secondary melanotic sarcoma (Hektoen and Herrick¹). In Eggel's 163 collected cases of primary carcinoma ascites occurred in 58·5 per cent. The obstructed portal circulation thus resembles that in portal cirrhosis, and an attempt at compensation by dilatation of the veins at the lower end of the oesophagus may result.

In a case under my care of secondary melanotic sarcoma of the liver which weighed 16 pounds, there were markedly varicose veins at the lower end of the oesophagus. Frerichs² records a similar case.

Portal thrombosis due to an extension of the growth from the intra-hepatic branches into the trunk of the portal vein may also account for ascites, but it is usually due to concomitant malignant disease of the peritoneum or to local inflammation of the capsule of the liver set up by an underlying growth. My own impression is that ascites is more frequent in secondary than in primary malignant disease of the liver. *df*) Eggel, however, estimates that ascites occurs in 58 per cent of the primary cases.

The ascitic fluid is usually serous and clear, like that in cirrhosis or in simple chronic peritonitis, but is bile-stained when there is jaundice. The effusion may be blood-stained from extravasation of blood into the growths, especially when they are necrotic and have ruptured into the general peritoneal cavity. In some cases, especially in sarcoma, the loss of blood, due to extravasation into the growths, may be so excessive as to give rise to faintness and collapse, while at the same time there is marked increase in the size of the hepatic tumour, which may even fluctuate and imitate very closely hepatic abscess (Byrom Bramwell,³ Hawthorne⁴).

It has been stated that ascites is rare or even that it does not occur in melanotic sarcoma of the liver, but this is not borne out by the cases I have collected, for it was stated to be present in 10 of the 37 cases of secondary melanotic disease of the liver; and in at least four of the reputed primary melanotic growths of the liver there was ascites. Occasionally the ascitic fluid is of a dark colour, from the presence of melanin; more often it resembles ordinary ascitic fluid.

In a woman aged thirty-three who died with melanotic sarcoma of the liver there were 100 ounces of dark fluid in the peritoneal cavity and a pint of brown

¹ Hektoen and Herrick. *Am. Journ. Med. Sc.*, Phila., 1898, cxvi, 255.

² Frerichs. *Diseases of the Liver*, ii, 239, New Sydenham Soc., 1861.

³ Bramwell, B. *Lancet*, Lond., 1897, i, 170.

⁴ Hawthorne, C. O. *Clin. Journ.*, Lond., 1896, viii, 361

fluid in each pleura (*Middlesex Hosp. Rep.*, 1890-91, p. 278). Wickham Legg¹ and Senator² also recorded cases of brown ascitic fluid.

In melanotic sarcoma of the liver the ascitic fluid may be clear and yet contain cells with pigment granules inside them (Hektoen and Herrick). In a case under my care the ascitic fluid, though of the ordinary straw colour, contained melanogen, as shewn by the appearance of a dark ring on adding a watery solution of ferric chloride. On the other hand, Dr. Garrod tells me that in two similar cases with melanuria the ascitic fluid did not give the reaction.

In rare instances the ascitic effusion may be chylous as a result of transudation of chyle or even rupture of a lymphatic trunk, due to the pressure and obstruction exerted by a secondary growth in the course of the chyliferous trunks. A chyliform or fatty ascitic effusion, not due to the escape of chyle, but the result of fatty degeneration and disintegration of cells suspended in the peritoneal effusion, is not so rare. The fluid resembles chylous ascites to the naked eye, but differs from it microscopically in the size of the fat-globules, which are large and not in the fine emulsion characteristic of true chylous ascites. The oil-globules may be formed either in the cells of the growths and discharged into the peritoneal cavity, or in leucocytes. Corselli and Frisco³ suggest that in malignant disease of the peritoneum, toxic bodies are formed which induce degenerative changes in the cells suspended in the ascitic fluid and so lead to fatty ascites.

In a case in St. George's Hospital a fatty milky effusion drawn off during life was found at the necropsy to be associated with numerous secondary growths in the liver, which weighed 15 pounds; there was also a large growth invading the receptaculum chyli, but no rupture of lymphatic vessels was forthcoming. The primary growth was in the gall-bladder.

In other cases there is milky ascites in which the opalescence is not due to fat but to the presence of a protein derivative or lecithin.

In a case of secondary carcinoma in a cirrhotic liver recorded by Achard and Laubry⁴ the amount of fat—0.6 per cent—was too slight to account for the milkiess of the ascites.

The leucocytes in the ascitic fluid may be so numerous as to suggest a purulent ascitic effusion although there is no peritonitis (Gentès⁵). As the result of perforation of a viscus or infection, however brought about, an ascitic effusion in hepatic carcinoma may be genuinely purulent.

The blood shews diminution of the red cells, with a more marked diminution in the amount of haemoglobin—a secondary anaemia. Leuco-

¹ Legg. *Trans. Path. Soc.*, Lond., 1878, xxix, 225.

² Senator. *Charité-Ann.*, Berlin, 1890, xv, 261.

³ Corselli e Frisco. *Riforma med.*, Roma, 1896, iv, 630.

⁴ Achard et Laubry. *Bull. et mém. Soc. méd. des hôp. de Paris*, 1902, 3. s., xix, 335.

⁵ Gentès. *Journ. de méd. de Bordeaux*, 1899, xxix.

cytosis may be present, but is not constant, and may be intermittent. It is usually moderate, but it may reach 36,000.

In 53 cases examined by Cabot¹ leucocytosis was present in 29. According to Da Costa² leucocytosis is more marked in hepatic carcinoma than in carcinoma of other organs.

The *urine* is usually diminished in amount, and occasionally shortly before death there may practically be suppression. It is high coloured, as a rule, and often lithatic, and may have a rather high specific gravity. When there is jaundice, bile-pigment is usually found in the urine, but when the jaundice is very slight, the urine may be acholic. When jaundice is marked, casts are found on centrifugalising the urine. Urobilin is present, sometimes in excess, unless the entrance of bile into the duodenum is entirely prevented. Indican is sometimes present.

Albuminuria is rare, and its presence in a doubtful case is in favour of some other condition, such as lardaceous disease, renal tumour, cystic disease, or hydronephrosis. It may, however, be induced by pressure on the inferior vena cava either by the liver or by enlarged glands. When the liver is so extensively infiltrated with growth that it is unable to stop poisons absorbed from the alimentary canal, the action of these poisons on the kidneys may result in albuminuria. In biliary obstruction with absence of bile from the intestines excessive fermentation may give rise to auto-intoxication and so to albuminuria. Teissier³ described this "hepatogenous albuminuria." As already pointed out, albuminuria is rare in malignant disease of the liver, while these disposing conditions—hepatic insufficiency and jaundice—are fairly common; it would, therefore, appear that some other factor is necessary to produce albuminuria; the requisite factor is probably some primary feebleness or want of tone in the kidneys. Transient haematuria, on one or more occasions, may be the only indication that the primary growth is in the kidney. Hydronephrosis may in rare instances be due to the pressure of the greatly enlarged liver on the right kidney (Litten⁴). When the liver is extensively infiltrated with growth, the amount of urea may be diminished, and leucine and tyrosine have been found in the urine, probably from cell-destruction.⁵

Sugar is not found in the urine in uncomplicated cases of malignant disease of the liver. In this connexion it is interesting to note that Warthin⁶ and Ohlmacher⁷ found hypertrophy of the islands of Langerhans which they regarded as a compensatory mechanism for the

¹ Cabot. *Clinical Examination of the Blood*, p. 440, 1904.

² Da Costa. *Clinical Hematology*, p. 388, 1902.

³ Teissier. *Semaine méd.*, Paris, 1899, xix, 282.

⁴ Litten. Quoted in *Semaine méd.*, 1892, xii, 80.

⁵ Compare Ulrich. *Nord. med. Ark.*, 1896, No. 11.

⁶ Warthin. *Phila. Med. Journ.*, 1900, vi, 124.

⁷ Ohlmacher, J. C. *Amer. Journ. Med. Sc.*, Phila., 1904, cxxviii, 287.

Weinberg and Mello reported 6.6 per cent of
eosinophils.

and the amount is a
measure of the malignancy
of the growth

Eppinger argues that a normal liver
destroys any melanin that gets into
the circulation, and that it is therefore
only when the liver is extensively
involved that it becomes unable to
prevent melanuria.

Peters recorded melanin without any
melanotic growth in a dark-skinned
boy with advanced hepatic cirrhosis.

Eppinger. Biochem. Zeitsch., Berlin, 1910, xxviii, 181.
PETERS, J.P. Arch. Int. Med., Chicago, 1923, xxxii, 709

impaired hepatic function in their cases of extensive growths in the liver.

Creatine, which is not present in normal urine, has been found in large amounts in the urine of patients with malignant disease of the liver (Mellanby¹).

In melanotic sarcoma the pigment melanin may appear in the urine (melanuria). The urine, when passed, is generally of the ordinary colour and gradually darkens on standing and exposure to the air. This darkening may be brought about rapidly by the addition of an oxidising agent, such as bichromate of potassium or nitric acid. A delicate test for melanin in the urine is the addition of a solution of ferric chloride, which even in dilute solutions produces a black colour. In very rare instances the urine is said to be black or dark brown when passed from the bladder. When the urine darkens after being passed the pigment is in the form of a colourless chromogen—melanogen—which by oxidation yields melanin. The melanin from the growth passes into the circulation, and may either be excreted as such, blackening the urine, or it may be changed by the tissues into melanogen and not produce any very manifest alteration in freshly passed urine. Melanuria may thus escape notice unless the urine is kept for a time or acted upon by oxidising agents. Nepveu and Chausel described pigment-granules in the blood and in the urine of patients with melanotic sarcoma.

In a man, aged fifty-nine years, under my care in St. George's Hospital, there were extensive melanotic sarcomatous growths in the liver, which weighed 16 pounds. The primary growth was a melanotic sarcoma of the eye removed twenty months before at Moorfields; the urine was clear when first passed, but darkened on standing and on the addition of nitric acid or ferric chloride.

Melanuria seldom occurs in the absence of secondary growths in the liver. The reasons for this probably are: (i) That there must be a considerable area of growth to provide a sufficiency of the pigment, and (ii) that the liver is more or less involved in most cases of generalised melanosis.

In one of the earliest cases described in this country as melanuria there was no hepatic growth (Hilton Fagge²). Melanuria was present in a case in which a large mass of melanotic growth occupied the left side of the chest, the liver being normal (Langdon Brown³).

The occurrence of melanuria does not depend on the presence of secondary growths in the kidneys and urinary tract, or on the kidneys being healthy, for it has been observed when the kidneys shewed the changes of arteriosclerosis. In some cases melanuria has been said to be intermittent.

The presence of melanin or of melanogen in the urine may be of great

¹ Mellanby. *Journ. Physiol.*, Cambridge, 1907, xxxvi; *Proc. Physiol. Soc.*, p. xxiii, *Brit. med. Journ.*, 1913, ii, 40.

² Hilton Fagge. *Trans. Path. Soc.*, Lond., 1877, xxviii, 172.

³ Brown, L. *Clin. Journ.*, Lond., 1909-10, xxxv, 191.

use in arriving at an accurate diagnosis in a case of enlarged liver. Thus in cases in which the primary growth in the eye remains latent, melanuria would shew that the enlargement was due to a melanotic growth. It has been¹ stated that melanin occurs occasionally in the urine in cases in which no melanotic growth is present, ~~but this is a mistake and is due to large quantities of indican in the urine (Garrod¹)~~. Urines which contain an excess of indican give with HNO_3 a reaction like that for melanin, but there is no colour reaction with ferric chloride, and in this way the two can be distinguished. The spontaneous darkening of the urine must be distinguished from that of alcaptonuria by the tests already given. In addition, alcaptonuric urine reduces Fehling's solution, but does not contain sugar, as shewn by the phenyl-hydrazine test. The toxicity of the urine has been stated to be increased (Charrin²).

Oedema of the feet is comparatively frequent in the later stages of the disease. It may be due to several causes, such as cardiac debility, or to toxæmia resulting from hepatic insufficiency; in the latter case the oedema is analogous to that in cirrhosis. Oedema, not only of the legs, but of the genitals, scrotum, and lower part of the trunk, may be mechanical and due to direct pressure exerted by growth, either in the liver or in the adjacent lymphatic glands, on the inferior vena cava and other venous channels, or to thrombosis of the inferior vena cava (*vide* case on p. 523), the iliac, femoral, or saphenous veins. Pheasants³ collected 3 cases in which malignant disease of the liver extended into the inferior vena cava. It may also be due to the pressure of ascites on the inferior vena cava.

Thoracic Signs.—The large liver may encroach on the thorax and thus lead to collapse and hypostatic engorgement of the bases of the lungs, with signs of bronchitis. Concomitant ascites will tend to displace the thoracic viscera and to compress the lungs and produce pulmonary embarrassment; this may be temporarily relieved by tapping the abdomen. When the growth involves the capsule of the liver or the diaphragm, symptoms of pleurisy may result. Infection of the pleura may give rise to an effusion, usually blood-stained, and in very rare instances purulent. There may be reflex cough. Enlarged glands, infiltrated with growth, may be palpable above the clavicles, especially on the left side, the infection being conveyed by the thoracic or by the right lymphatic duct (compare Stevens⁴).

Symptoms.—Great weakness is not infrequent. It may be the result of such extensive destruction of the liver substance that the organ fails to stop poisons which in the ordinary course of events are absorbed from the alimentary canal and then destroyed or rendered innocuous. This hepatic inadequacy leads to general toxæmia and so to great feebleness. Hepatic inadequacy would also interfere with the absorption and proper

¹ Garrod. *St. Barth. Hosp. Rep.*, 1902, xxxviii, 25.

² Charrin. *Semaine méd.*, Paris, 1892, xii, 80.

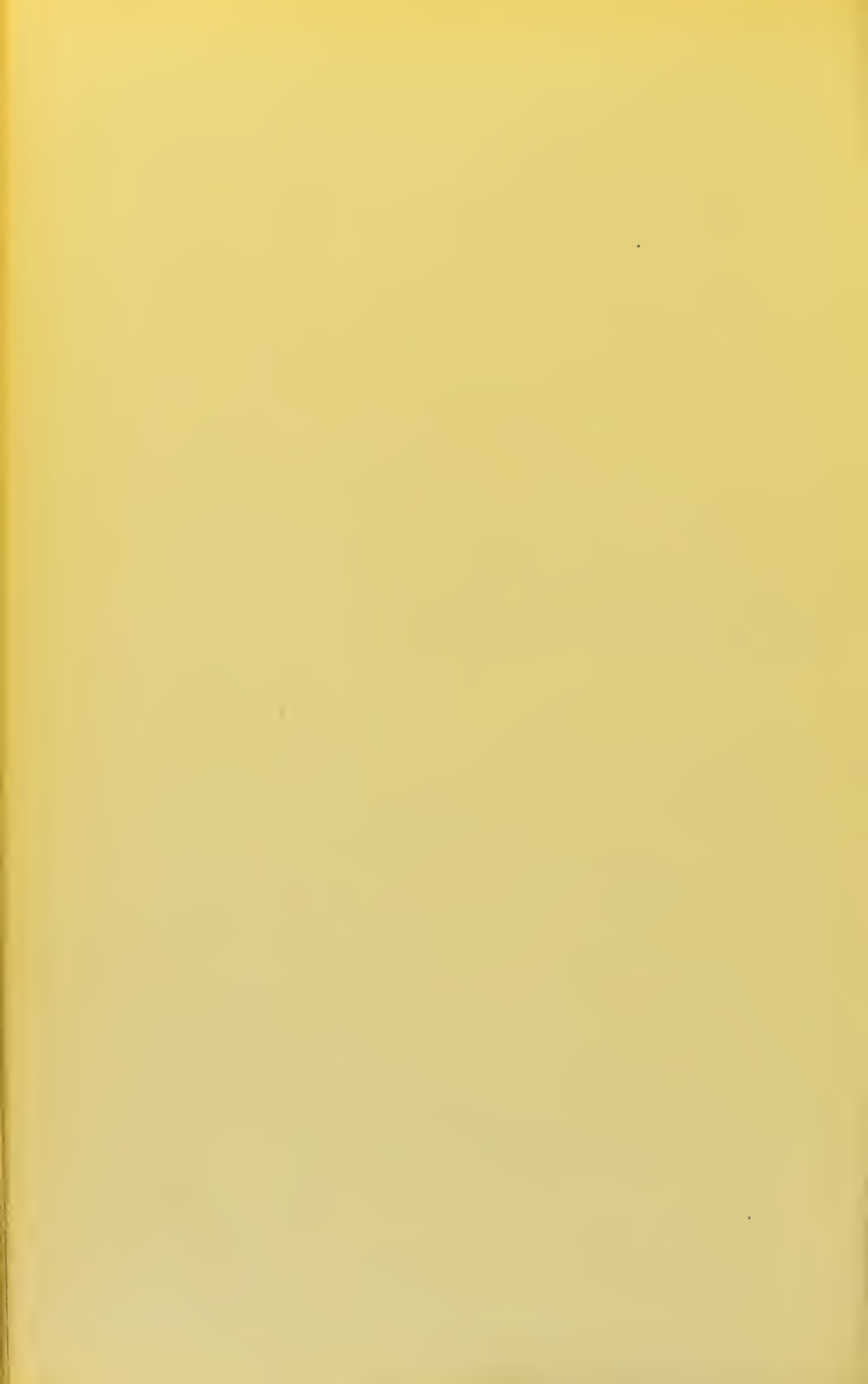
³ Pheasants. *Bull. Johns Hopkins Hosp.*, Balt., 1909, xx, 292.

⁴ Stevens. *Brit. Med. Journ.*, 1907, i, 306.

especially in intestinal obstruction with a high non protein nitrogen
and low chloride content of the blood (Haden and Orr)

HADEN, R. L. and ORR, T. G. Johns Hopkins Hosp. Bull., Baltimore, 1924, XXXV, 58

~~PETER, J. P. Arch. Int. Med., Chicago, 1923, XXXII, 709.~~



assimilation of food. In many instances a primary growth in the alimentary canal impairs nutrition and so accounts for asthenia.

Gastric disturbance is common, there being loss of appetite, or even a marked distaste for food, especially for meat. In very rare instances there is great exaggeration of appetite, while in some cases the appetite remains unaffected or is sustained by a sort of auto-suggestion to counteract the wasting (Hanot¹). Nausea is often present, and there may be vomiting. Spasmodic dysphagia, reflex in origin, has been reported. Chronic gastritis may for a time be the chief or only manifestation. The bowels are usually confined, and in the late stages it may be difficult to get them to act without disturbing the patient too much. Diarrhoea may be due to a primary growth in the colon. In the late stages obstinate hiccup may supervene; and thrush may invade the mouth and render swallowing difficult. I have seen the whole oral cavity lined by bile-stained thrush resembling wash-leather.

Hepatic pain may be caused by tension and stretching of the capsule, due to the presence of rapidly increasing tumours in the liver; but pain is mainly caused by perihepatitis set up by growths involving the capsule of the liver; in some instances sudden acute pain due to perihepatitis may be the first symptom. When the growth is deep-seated in the substance, as in some examples of primary carcinoma, pain may be slight or even absent throughout. Pain may be almost constant in the right hypochondrium, but is often especially felt in the back, in the shoulder, or in the loins, and may run down the right arm. It is more marked on exertion, and is worse at night. Pain is not present in all cases; but it has some bearing on the diagnosis, since there is comparatively little pain in cirrhosis, while in malignant disease of the liver pain may be persistent. Secondary growths in the diaphragm or an extension of the growth from the liver into the diaphragm may set up pleurisy and so cause a good deal of pain. Attacks of pain resembling those of biliary colic, but not due to gall-stones, are occasionally met with when the common duct is pressed upon from without.

V. Schultz² described attacks of false gall-stone colic in a man, aged forty-seven, due to secondary growths in the portal fissure which compressed the duct and set up jaundice. The primary growth was in the rectum.

Pruritus, or itching of the skin, may be very troublesome, and a patient who is semicomatose may be continually scratching himself. It is usually associated with jaundice and occurs comparatively late in the course of the disease. Bouchard³ speaks of it as sometimes present early in the disease, before sufficient data for the diagnosis are forthcoming.

It is very seldom that *peripheral neuritis* can be referred solely to failure of the detoxicating function of the liver. Most cases of

¹ Hanot. *Mercure médical*, Paris, 1893, iv, 417.

² Schultz. *Berlin. klin. Wochenschr.*, 1894, xxxi, 132.

³ Bouchard. Congress at Rome, 1894.

peripheral neuritis complicating malignant disease of the liver are due to alcoholism.

Hayem¹ observed the acute onset of neuritis in both arms and legs in a case of primary carcinoma of the liver, which may have been due either to hepatic insufficiency or possibly to toxins derived from the growth.

In primary malignant disease the liver may be so extensively infiltrated with the growth that hepatic insufficiency is established. This accounts for the occurrence of haemorrhages, somnolence, and delirium in the last stages, and may render the diagnosis from cirrhosis difficult.

Charrin² described a case in which mental delusions occurred in an early stage of carcinoma of the liver and were thought to be due to toxæmia, as the toxicity of the urine was increased.

Duration.—Primary malignant disease of the liver runs a rapid course, and sometimes justifies the descriptive title "acute cancer."³ From an analysis of his cases Hale White⁴ concluded that the disease probably never lasts more than four months. In exceptional cases symptoms do not exist for as many weeks. The disease may remain latent; and in two instances there has been a history, possibly untrustworthy, of illness for a week only before death (Karsner⁵).

In secondary malignant disease of the liver the duration of life varies. Much depends on the nature and situation of the primary tumour, which may kill the patient before the growths in the liver have become manifest. On the other hand, if the primary growth has been removed or remains entirely latent, life may be prolonged for a year or even longer, after signs of a tumour in the liver have appeared. Usually, however, death occurs within six months of the first sign of hepatic enlargement.

Christian⁶ reported a case of carcinoma of the liver secondary to an almost latent columnar-celled growth in the rectum, in which the liver was enlarged below the umbilicus thirty-five months before death. Taylor⁷ mentions a case of three years' duration.

Sometimes the liver may be considerably enlarged and nodular, and the patient remains for weeks in much the same condition and then suddenly goes rapidly downhill. In other instances the liver steadily enlarges, and the patient's condition deteriorates. It has been stated that secondary growths in the liver grow with greater virulence during hot weather (Fenwick⁸).

¹ Quoted in Lévi's *Thèse de Paris*, 1896.

² Charrin. *Semaine méd.*, Paris, 1892, xii, 310.

³ Rioufol. *Thèse de Lyon*, 1899 (Acute Cancer of Liver).

⁴ Hale White. *Guy's Hosp. Rep.*, 1890, xlvii, 59.

⁵ Karsner. *Arch. Int. Med.*, Chicago, 1911, viii, 238.

⁶ Christian, H. A. *Am. Med.*, Phila., 1903, v, 131.

⁷ Taylor, F. *Clin. Journ.*, Lond., 1912, xl, 17.

⁸ Fenwick. *Cancer and Other Tumours of the Stomach*, p. 183, 1902.

In Ribadeau-Dumas and De LAULIERA's case
of 5 years' duration it was assumed that there
was first an adenoma which eventually
became malignant.

Weber reported rupture of
a chorion epitheliomatous
growth in the liver secondary
to the testis with intraperitoneal
hemorrhage.

Weber, R.P. Practitioner, 1910, C1, 31.

Termination.—Death usually occurs from increasing asthenia and in coma, the patient often being unconscious for one or more days before the end comes. Sudden death has been known to occur while the patient is still well nourished.

Lambert¹ reported a case with fatal intraperitoneal haemorrhage from a secondary nodule of carcinoma in the liver; the immediate cause was thought to be straining in sea-sickness. A girl aged sixteen years was admitted into St. George's Hospital in 1911 with acute abdominal symptoms which came on after sitting up. Laparotomy revealed a large quantity of blood in the peritoneal cavity. At the necropsy the liver, which was full of peritheliomatous nodules and weighed 6 pounds, shewed a rent 4 inches long antero-posteriorly.

DIAGNOSIS.—The diagnostic signs of malignant disease in the liver are rapid and progressive enlargement, with evidence of definite tumour formation in the organ, pain, loss of weight and of constitutional strength, and, when the disease is not primary in the liver, evidence of malignant disease elsewhere. As pointed out already, the primary growth is latent in about half the cases of secondary malignant disease of the liver.

As a rule, malignant tumours of the liver, whether primary or secondary, give rise to some hepatic enlargement and pain, so that disease of the liver is at least suspected. When the growths are small and the liver is not enlarged, there may be no clinical evidence that the liver is affected; in such cases the patient dies from the effects of the primary growth.

In primary malignant disease of the liver the growth rarely remains entirely latent. It may, however, happen that the observer's attention is exclusively directed to secondary results or concomitant affections.

Sokoloff² described the case of a man aged seventy who had ascites and dropsy and was regarded as having arteriosclerosis. After death a primary columnar-celled carcinoma of the liver was found. Gouget³ narrated a very similar case in a man aged fifty-three years, thought to have arteriosclerosis and bronchitis. At the necropsy the liver was of normal size and contained numerous growths of columnar-celled carcinoma; there were no growths in the body. H. G. Wells⁴ reported a case of primary carcinoma with cirrhosis which was latent, the patient dying from uraemia. Hale White⁵ recorded the case of a woman aged thirty-nine, thought to be suffering from the vomiting of pregnancy, who died after premature labour had been induced. Primary malignant disease of the liver, which weighed 126 ounces, was found. A man, aged sixty, after pain in the epigastrium, gradually passed into a condition suggesting general paralysis of the insane; at the necropsy there was a primary massive carcinoma of the liver and innumerable secondary growths in the brain and cerebellum (Giachetti⁶).

¹ Lambert. *Brit. Med. Journ.*, 1908, i, 81.

² Sokoloff. *Virchows Arch.*, 1900, clxii, 1.

³ Gouget. *Bull. Soc. Anat.*, Paris, 1898, lxxii, 605.

⁴ Wells, H. G. *Am. Journ. Med. Sc.*, Phila., 1903, cxxvi, 403.

⁵ Hale White. *Trans. Path. Soc.*, Lond., 1885, xxxvi, 251.

⁶ Giachetti. *Riv. di patol. nerv.*, Firenze, 1907, xii, 149.

Differential Diagnosis.—The diagnosis of malignant disease in the liver substance, whether primary or secondary, from other conditions will first be considered, and then the distinction between primary and secondary malignant disease will be dealt with.

Portal Cirrhosis.—When a patient comes under observation with the abdomen full of ascitic fluid it is often difficult to decide whether there is cirrhosis in a late stage or malignant disease of the liver. The diagnosis must then remain in doubt until the fluid is withdrawn; when this has been done, the liver can be carefully examined. A small or moderately enlarged liver, when associated with enlargement of the spleen, points to cirrhosis; a large and nodular liver, especially when combined with umbilication of the surface, indicates malignant disease. Emaciation and pain are more prominent in malignant disease, but wasting may be very considerable in cirrhosis. A large cirrhotic liver, when associated with some jaundice and ascites, closely imitates carcinoma, but the enlargement is more uniform and affects both lobes, the spleen is often enlarged, and cachexia is less rapid. The association of ascites and well-marked jaundice, however, should suggest malignant disease. Progressive increase in size is in favour of growth, more especially if it affect one lobe only. Δ In the following case primary carcinoma imitated cirrhosis: .

A cook aged forty-three years was admitted into St. George's Hospital with vomiting in the morning, loss of appetite, and emaciation. She had had piles for fifteen years. Alcohol had been taken in moderation. She was thin, had an enlarged, roughened liver, and some ascites which rapidly increased and required tapping. She became jaundiced and passed into a "typhoid" condition. At the necropsy, except for a few minute nodules in the lungs, there was no new growth in any part of the body, except in the liver, which weighed 106 ounces; there was no tumour in the gall-bladder or ducts; the right lobe contained extensive areas of whitish-yellow growth of firm consistency, and also small umbilicated nodules; the left lobe was a thin cake of about the size of a child's hand, and was nearly separated from the rest of the liver, and moved as if on a hinge; it also contained much growth. The liver was not cirrhotic. There was chronic gastritis.

In primary carcinoma supervening on cirrhosis, a diagnosis from cirrhosis is usually impossible, unless the liver is large and nodules of growth can be felt. Pain over the liver is often more prominent in these cases than in cirrhosis, and jaundice, though not always present, may be considerable.

From the large liver of *hypertrophic biliary cirrhosis* primary malignant disease differs in its more rapid growth, in the absence of splenic enlargement, and in the character of the jaundice. In malignant disease it is, generally speaking, either absent or, if present, obstructive, so that no bile passes into the blood. In biliary cirrhosis jaundice is constant, but not complete, and the faeces are not colourless. Hypertrophic biliary cirrhosis is met with much earlier in life than malignant disease.

Syphilis of the Liver.—Gummatous enlargement, especially when the

^ Splenomegaly does not occur in ^{uncomplicated} malignant disease of the liver, except in ~~the~~ primary carcinoma with cirrhosis, and is therefore against this diagnosis. Hawthorne who has collected examples to this rule, points out that enlargement of the left lobe of the liver, a growth near the spleen, or a primary carcinoma of the fundus of the stomach may be mistaken for the spleen.

Hawthorne. Edin. Med. Journ., 1901

According to Verdozzi and Urbani
a positive Wassermann reaction
occurs in malignant neoplasms
of the liver without any other
evidence of syphilis.

VERDOZZI and URBANI. Polichin, Roma
1915, sez. med., XXII,

patient is cachectic, may suggest malignant disease. When the liver is hard and enlarged and the patient's general condition is good, gumma should be thought of and vigorous antisyphilitic treatment should be employed. In all cases of doubt iodides in large doses and mercury should be given. If, after a full course, the enlargement is still progressive, the case is almost certainly malignant. A history of syphilis and a positive Wassermann reaction are, of course, important, but the most decisive point is the effect of antisyphilitic treatment adequately carried out.

A large, firm, *lardaceous liver* in a cachectic patient might be mistaken for primary massive carcinoma of the liver at first sight, but the evidence of lardaceous disease elsewhere, as shewn by albuminuria and diarrhoea, the absence of pain and of rapid and progressive enlargement of the liver, together with a history of past suppuration or of syphilis, should lead to a correct diagnosis. A lardaceous liver with gummatous change or cicatrices may be so large and nodular that secondary malignant disease is closely imitated. The history and evidence of syphilis are important, but the effect of treatment is the only means of definitely deciding the point; if the liver progressively enlarges under full doses of iodide of potassium, malignant disease is almost certainly present. Other evidences of lardaceous disease, such as albuminuria, should also be looked for. Albuminuria is decidedly rare in malignant disease.

A *hydatid cyst* may suggest malignant disease of the liver, especially a primary massive carcinoma, in a comparatively early stage before constitutional symptoms have arisen; and multiple hydatid cysts may simulate the nodules of secondary malignant disease.

In hydatid the enlargement is slow and constitutional symptoms are absent. In malignant disease the tumour usually grows rapidly, other nodules may be felt, and cachexia is likely to supervene. Malignant disease occurs later in life than hydatid cyst of the liver; caution is, therefore, necessary before diagnosing hydatid in elderly persons. When the liver contains several hydatid cysts, some difficulty in arriving at a correct diagnosis must be expected.

In a case diagnosed as hydatid of the liver and operated upon, the appearances so closely resembled multiple malignant growths that the operation was abandoned; at the necropsy they were found to be multiple hydatids (Sargnon¹). The coincidence of carcinoma and hydatid cysts in the same liver is referred to on p. 397.

Alveolar or multilocular hydatid has often been mistaken for malignant disease, both clinically and even when found after death. It has not been recognised in Great Britain. In most cases the spleen is enlarged, and its course is much slower than in malignant disease.

Cystic disease of the liver may cause very great enlargement. Considerable cystic change in the kidneys is nearly always present and the kidneys may be palpable. The condition is very chronic, and the symptoms are renal rather than hepatic.

¹ Sargnon. *Lyon méd.*, 1898, lxxxvii, 254.

Hepatitis due to chronic malarial infection occasionally gives rise to difficulty in diagnosis at first. But the history, examination of the blood, and the effect of quinine should clear up any doubt.

Influenzal hepatitis is not common, but it may closely imitate the early stages of malignant disease of the liver. The enlarged liver is accompanied by some fever, and a cautious opinion must be expressed until the course of events has been watched.

Intrahepatic Suppuration.—In rare instances the soft character of a rapidly growing tumour, or the formation of false cysts from necrosis or haemorrhage, may give rise to fluctuation, while fever, which is not very uncommon in malignant disease of the liver, may increase the resemblance to some form of intrahepatic suppuration, such as abscess and pylephlebitis; this is especially so in primary sarcoma of rapid growth in children or young adults. An exploratory laparotomy may be the only means of distinguishing between growth and suppuration. Suppuration may indeed be superimposed on malignant disease.

A man aged forty-one years began to suffer from sick headaches three months before his death; a month later he had flatulence and epigastric pain. When admitted into St. George's Hospital the patient, who was well nourished and free from jaundice, presented great enlargement of the liver, which projected markedly in the epigastrium. After admission the temperature became raised, and, an abscess being suspected, the liver was aspirated, but nothing but blood was withdrawn. As the temperature continued to rise, laparotomy was performed, and numerous growths on the surface of the liver were found. A small piece was removed, and found to be a spheroidal-celled carcinoma. The patient died a week later. At the necropsy the liver weighed 11 pounds 7 ounces; the left lobe was almost uniformly infiltrated by new growth, and the right lobe contained a number of discrete tumours. The only other growth was one in the middle of the body of the pancreas. Howard Marsh¹ reported the case of a soldier aged forty-three, who had been in India, and had an enlarged liver extending two inches below the ribs and forming a prominent swelling in the epigastrium, with exactly the appearance of an abscess pointing; it was soft, fluctuating, and the skin over it was dusky-red. Aspiration only brought away a little blood, and at the necropsy cancer of the liver was found. In Bramwell and Leith's² case an abscess was diagnosed and 53 ounces of chocolate-coloured fluid were removed by aspiration. There was a primary, irregular-celled sarcoma of the liver, which weighed 9 pounds. Hawthorne³ published a somewhat similar case.

In the following case there was some resemblance to pylephlebitis:

A man aged twenty was admitted under my care at St. George's Hospital with anaemia, fever, and a large and tender liver. His history pointed to an attack of appendicitis five weeks before, followed by two rigors and by vomiting. It was thought that he had either a large appendicular abscess tracking up to the liver by the side of the colon, or pylephlebitis. At the operation there was

¹ Marsh, H. *St. Barth. Hosp. Rep.*, 1887, xxiii, 148.

² Bramwell and Leith. *Lancet*, Lond., 1897, i, 170.

³ Hawthorne, C. O. *Clin. Journ.*, Lond., 1896, viii, 361.

no abscess, but the liver was large and bled readily when punctured ; on the convexity of the liver there was a raised area, thought to be either an early stage of an abscess or new growth. It was punctured, but nothing came out. The age of the patient militated against new growth. The patient survived for five weeks ; during the greater part of this period the temperature was intermittent, going up to 101° at night and becoming normal in the morning ; during the last week of life the temperature was almost normal. Oedema of the legs and back developed some weeks before death. At the necropsy the liver was occupied by numerous white growths shewing cystic degeneration, and weighed 18 pounds. The primary growth was in the left kidney. There was thrombosis of the inferior vena cava close to its bifurcation, thus accounting for the oedema. The portal vein was normal. Microscopically the growth was an endothelioma.

A large cystic sarcoma of the liver, such as that described on page 522, may very closely imitate an abscess or a sanguineous peritoneal cyst.

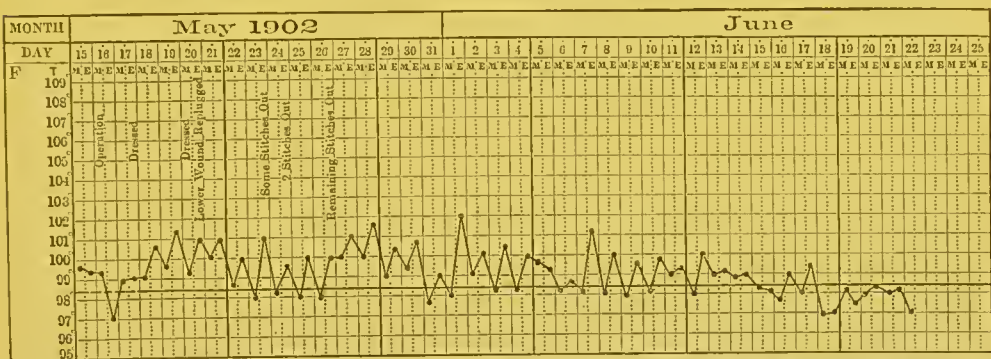


FIG. 77.—Temperature chart of a man, aged twenty years, with secondary endothelioma of liver imitating pyelophlebitis. Primary growth in the left kidney.

If opened, the fluid from a cystic sarcoma will probably contain growth when examined microscopically, but even then it may be impossible to say whether the growth arose in the liver or invaded it, as a suprarenal or other retroperitoneal tumour might do. The diagnosis during life in these cases is extremely difficult. Conversely, slow abscess formation in the liver may be regarded as malignant disease and not operated upon for this reason.

Chronic Venous Engorgement.—The enlarged and tender liver of chronic venous engorgement, especially in the late stage of mitral disease, has, in rare instances, been regarded as malignant. This mistake is not likely to occur often, as the general aspect of the two diseases is so different. Difficulty is more likely to arise in cases of marked dilatation of the left ventricle without any mitral murmur. The presence of obstructive cardiac or pulmonary disease, and the effect of treatment by digitalis, strophanthus, purgatives, etc., in diminishing the size of the liver are points in the diagnosis on which further insistence is unnecessary.

A woman, aged forty, but looking fifteen years older, was under my care in St. George's Hospital with great pain and respiratory distress. Her appearance

suggested morbus cordis or a large pleural effusion, but the heart appeared healthy and there was only a little dulness at the right base. There was much resistance in the epigastrium and great pain on pressure, and as she had frequent retching, it was thought she might have malignant disease of the stomach and liver. Her condition prevented a thorough examination, and she was kept under the influence of morphine, but the pain seemed very severe. Three days before death she became jaundiced. At the necropsy there was no growth of any kind. The liver was enlarged and shewed some, but not advanced, chronic venous engorgement. The heart, 15 ounces, shewed extensive fibroid disease. The orifices of the coronary arteries were extremely small, and the ascending part of the aorta shewed gelatinous thickening, suggesting syphilitic or acute aortitis. There were a pulmonary apoplexy in the right lung and a pleural effusion. It is probable that the pain was cardiac and of the nature of angina.

In a girl, aged three and a half years, under my care a large firm liver was thought to be sarcomatous. The heart appeared normal and after death did not shew any disease. The liver shewed advanced chronic venous engorgement, the causation of which was obscure.¹

Gall-stone in the Common Bile-duct ; Intermittent Hepatic Fever.—Impaction of a gall-stone in the common bile-duct may occur without previous attacks of biliary colic. When this occurs in a person past middle life, it may be regarded as malignant disease of the liver, especially the form arising in the bile-ducts (*vide* p. 689). As time goes on, however, the jaundice tends to diminish, whereas in malignant disease it becomes deeper. In impacted gall-stone the liver, if enlarged at first, does not progressively increase in size, but rather diminishes, and there is an absence of irregularities on its surface.

A man aged sixty-seven became jaundiced at the beginning of 1890 after having felt weak for ten days ; there had been no pain or colic. About May 17 he consulted the late Sir Andrew Clark, who, according to the patient, diagnosed cancer of the liver and gave him a month to live. When admitted to St. George's Hospital he was thin, jaundiced, and weak. The hepatic dulness began at the fifth rib in the right nipple line, and extended below the right costal margin, where there was a round, dull swelling extending downwards to within one inch of the umbilicus. No pain or tenderness existed. With rest in bed the jaundice cleared away and the tumour in the right hypochondrium receded, until, at the beginning of August, the skin was almost natural in colour. He then had spells of diarrhoea, which, however, were easily controlled by treatment. In September and October he had rigors on two occasions and fever at intervals, and he was losing flesh and strength from attacks of diarrhoea. On November 17 a severe bout of diarrhoea began ; on the 19th he had a rigor, and on the following morning he died rather suddenly. At the necropsy I found a large calculus in the common bile-duct, close to the duodenum ; it was loose and allowed bile to flow past it into the duodenum, as was proved by pressure on the gall-bladder. There was cholangitis, the liver shewed secondary pericholangitic fibrosis, and there were numerous adhesions around the gall-bladder and liver. There was no malignant disease in the body.

¹ Rolleston. *Trans. Med. Soc. Lond.*, 1909, xxxii, 19 ; and *Clin. Journ.*, Lond., 1908, xxxiii, 138.



A displaced or a wandering liver rarely imitates malignant disease. In Crawford's¹ case of anteverted wandering liver malignant disease was diagnosed during life. The association of jaundice and ascites with hepatoptosis is most unusual, but it may occur from kinking of the portal vein and bile-duct. The freely movable state of the liver should direct attention to the real condition. The severe constitutional symptoms in malignant disease and their absence in wandering and displaced livers should help to prevent any confusion.

A large *renal tumour* on the right side may appear to be in direct continuity with the liver. In some cases of extensive *cystic disease* of the kidneys the tumour may imitate a distended gall-bladder, or possibly, if tense cysts project from the surface of the kidney, secondary growths in the liver. A bimanual examination will shew that the renal tumour definitely bulges into the loin. The presence of bowel in front of the renal tumour is important; this may be made more manifest by filling the colon with air after removing its solid contents by means of an enema.

Tumours of the right suprarenal, by growing forwards, may closely resemble hepatic growths. In some cases the liver may be invaded by continuity, and secondary growths often occur in the liver.

In a large cystic sarcoma of the right suprarenal, which I examined post-mortem in 1891, the diagnosis was first hydatid of the liver, and subsequently malignant disease; there were secondary growths in the liver, as well as direct invasion of that organ.

Inflammatory thickening around the gall-bladder may be palpable as a hard mass, and thus may give rise to physical signs resembling carcinoma. The history of gall-stones and the fact that the patient's general state is not so grave as in carcinoma are important points to bear in mind.

Occasionally *faecal accumulation* in the transverse colon may imitate malignant disease; here the tumours may vary in position from time to time, can be indented by pressure, are capable of removal by purgatives or abdominal massage, and, when a careful examination is made, if need be under an anaesthetic, other masses can be made out in the course of the colon.

Improbable as it may appear, difficulty has arisen in distinguishing between *pregnancy* and secondary malignant disease of the liver.

In the following case² both conditions existed at the same time and the abdominal enlargement was naturally thought to be explained by pregnancy. A married woman aged thirty-nine years, who had had several children, was thought to be pregnant. She died, and a six-months fetus was found in the uterus. The liver weighed 17½ pounds and contained numerous secondary growths; the primary growth appears to have been in the colon. A case was reported by

¹ Crawford, R. P. *Lancet*, Lond., 1897, ii, 1182.

² Robinson. *Trans. Path. Soc.*, Lond., 1850, ii, 167.

Hale White¹ in which a woman was thought to be suffering from the vomiting of pregnancy until a primary carcinoma of the liver was found at the necropsy.

Diagnosis between Primary and Secondary Malignant Disease of the Liver.—In secondary malignant disease of the liver the primary growth may remain entirely latent during life. In such cases there are often no means of arriving at a correct diagnosis of secondary, rather than primary, malignant disease of the liver. These cases, which are clinically described as "malignant disease of the liver," tend, when included in statistics, to make primary malignant disease appear less rare than it really is. In about half the cases of secondary carcinoma of the liver the primary site cannot be determined during life. The primary growth may remain latent when it is in the stomach, pancreas, oesophagus, kidney, and, in exceptional instances, when in the colon.

A wasted old man aged sixty-two years was admitted under my care in St. George's Hospital on June 22, 1899, complaining of pain over the liver, inability to lie on his left side, shortness of breath, difficulty in digestion, and constipation. Six weeks previously his legs began to swell; this was followed by swelling of the abdomen. He had ascites which required tapping. The liver was much enlarged and extended nearly down to the umbilicus; nodules which seemed to be umbilicated were readily felt. On the skin over the free edge of the liver there was a meshwork of dilated vessels. There was dulness in both flanks. The urine was free from albumin; two days before his death, when his conjunctivae became jaundiced, bile-pigment appeared in the urine. He got steadily weaker, had little or no pain, completely lost his appetite, and died after being in a drowsy condition for forty-eight hours on July 6. At the necropsy the liver weighed 9 pounds 14½ ounces, and was packed with nodules of soft white growth which were not umbilicated. The right kidney weighed 8 pounds 5½ ounces, and was transformed into a large haemorrhagic growth which had broken down into pseudo-cysts. Some of the cysts contained cholesterol crystals. Microscopically the tumour was a perithelioma (*vide* Fig. 71). Kely-nack² described a somewhat similar case in a woman, but the left kidney was affected and there was haematuria, so that the primary growth did not remain latent. The liver contained numerous cystic tumours and weighed 111 ounces. I have seen two other cases in which the primary growth in the kidney remained quite latent; this is very likely to happen when the right kidney is affected and is under cover of the enlarged liver, but it may occur when the growth in the left kidney is small.

From extreme sensibility and a mistaken sense of delicacy a woman may conceal a carcinoma of the breast and only complain of symptoms pointing to malignant disease of the liver.

Such a case is recorded by Pearson and Howes³ in which an ulcerating carcinoma of the mamma was only discovered after death in a woman aged sixty who during life had been under treatment for a tumour in the liver with pain and ascites.

¹ Hale White. *Trans. Path. Soc.*, Lond., 1885, xxxvi, 251.

² Kely-nack. *Journ. Path. and Bacteriol.*, 1897, iv, 236.

³ Pearson and Howes. *Trans. Path. Soc.*, Lond., 1875, xxvi, 185.



Carcinoma of the stomach may remain quite latent when there are extensive secondary growths in the liver. According to Fenwick,¹ the changes in the liver are most marked when the tumour in the stomach is comparatively insignificant. Inasmuch as a pyloric growth is likely to lead to obstruction and symptoms, the latent growths are more often in the body or cardiac end of the stomach.

Secondary growths in the liver are not uncommon in carcinoma of the lower half of the oesophagus, but dysphagia is nearly always present.

In a man aged fifty-five years who died in St. George's Hospital with carcinoma of the oesophagus and numerous secondary growths in the liver, which weighed 14 pounds, there was nothing more definite than a distaste for solid food (*vide* p. 511).

The presence of an enlarged gland (Virchow's gland) above the clavicle should suggest the possibility of oesophageal carcinoma, but it may, of course, occur in other cases of generalised new growth. Enormous enlargement of the liver may be due to melanotic sarcoma secondary to a primary tumour in the uveal tract; in such cases the seat of the primary growth may easily be overlooked if the patient wears a glass eye and does not mention that his eye has been removed.

Multiplicity of nodules on the surface of an enlarged liver is much in favour of secondary growth, but unless there is definite evidence of primary neoplasm in the body, or of one having been removed, the diagnosis of secondary growths, though most probable, cannot be made with absolute certainty, since primary malignant disease may occur in a multiple nodular form. Deep jaundice and the association of ascites with jaundice are in favour of secondary malignant disease, whereas very rapid enlargement of the liver without emaciation is more frequent in primary malignant disease. It is true that the liver may increase in size very rapidly in secondary malignant disease, but since the primary growth is usually in the alimentary canal, there is generally considerable emaciation on this account before the liver is much or at all affected. When the primary growth is in the kidneys or in the uveal tract, emaciation is not so marked. In the enlargement of the liver due to melanotic sarcoma a clue to the nature of the disease, even in the absence of any history of an intra-ocular growth, may be obtained by the detection of melanin in the urine. To summarise the differential diagnosis of primary and secondary malignant disease of the liver:

<i>Primary.</i>	<i>Secondary.</i>
No sign or symptom of growth elsewhere in the body.	Some evidence of growth elsewhere.
A single tumour.	Multiple tumours.
Very rapid growth.	Less rapid growth.
Jaundice rare and slight.	Jaundice common.
Ascites not so frequent.	Ascites common.
Emaciation not so marked.	Emaciation marked.
Course rapid.	Course not so acute.

¹ Fenwick. *Cancer and Other Tumours of the Stomach*, p. 182, 1902.

Pepere¹ attempted to draw a clinical distinction between primary carcinoma and primary sarcoma of the liver on the grounds that primary sarcoma runs a more rapid course and is less frequently accompanied by jaundice or ascites than primary carcinoma. Bertelli² supports this distinction.

PROGNOSIS.—When the diagnosis of malignant disease of the liver can be made at the bedside, the prognosis is always hopeless. It is true that when laparotomy reveals the presence of early primary malignant disease of the liver, malignant disease limited to a constriction lobe, or malignant disease of the gall-bladder invading the liver, there is a chance that removal will not be followed by recurrence. But even in these cases, which can hardly be diagnosed with any certainty before the abdomen is opened, the disease usually returns and kills the patients. Operation for removal of malignant growths from the liver, whether from its substance or when starting in the gall-bladder, is the only means at our disposal at present of mitigating the otherwise absolutely fatal prognosis. The prognosis is better when a growth originating in the gall-bladder is removed than in resection of the liver for a primary neoplasm. Death is more rapid in primary malignant disease than in the more familiar secondary growths in the liver.

How long life may be prolonged with secondary growths in the liver is uncertain (*vide* p. 518). In most cases death follows within six months of definite evidence of hepatic enlargement. The size of the liver and the constitutional condition are valuable guides as to the time left to the patient. The onset of oedema of the legs usually means that the end is near. It must be remembered that in some instances the liver may have been previously enlarged from some independent cause; a floating lobe or tight-laced liver might thus give rise to a fallacy.

In a case of secondary melanotic sarcoma of the liver recorded by Litten there was evidence of hepatic enlargement for four years before death, a period quite incompatible with the view that a secondary growth was present all the time.

On the analogy of the spontaneous disappearance of solid and inoperable growths in the abdomen having the appearance of malignancy—a remarkable event to which Greig Smith³ drew attention—it is conceivable that malignant disease of the liver might occasionally disappear. In exceptional cases hepatic enlargement due to carcinoma has been noticed to pass away spontaneously (A. P. Gould,⁴ Hodenpyl⁵).

Campbell quotes a case⁶ in which influenza, supervening in the course of malignant disease of the liver, was followed by rapid diminution in the size of

¹ Pepere. *Arch. de méd. expér. et d'anat. path.*, Paris, 1902, xiv, 805.

² Bertelli. *Policlin.*, Roma, 1908, xxiv, 957.

³ Greig Smith. *Med.-Chir. Trans.*, Lond., 1894, lxxvii, 139.

⁴ Gould, A. P. *Clin. Journ.*, Lond., 1902, xx, 96.

⁵ ~~Hodenpyl. *Med. Rec.*, N.Y., 1910, lxxviii, 359.~~

⁶ Campbell, H. *Brit. Med. Journ.*, 1898, i, 1126.



145R
April
1921

Injection of the patient's own ascitic fluid
has in isolated cases been followed by
fibrosis of a carcinomatous liver (Hodenpyl, Ewing)

Hodenpyl. Med. Rec., N.Y., 1910, Lxxviii, 359
EWING. New York Med. Journ., 1912, XLV, 77.

the liver. The patient indeed seemed to get well, but in one-and-a-half years' time the growth returned and proved fatal. It is conceivable that in this instance a secondary streptococcal infection on the influenzal attack may have manufactured a toxin that acted on the hepatic growth, much in the same way as Coley's fluid does on sarcoma.

The only bright side to the prognosis of malignant disease of the liver is the possibility that the diagnosis may be wrong and that the actual condition is gummatous or hydatid disease of the liver.

TREATMENT.—**Medical treatment** is purely palliative, and directed chiefly to the relief of pain and discomfort by morphine, opium, aspirin, and chloral. Hypodermic injection of morphine is preferable to opium by the mouth, inasmuch as it is more surely absorbed, disturbs digestion less, and its effects can be more accurately estimated. From the necessarily fatal nature of the disease morphine may be given without any qualms of conscience as to morphinomania. Measures should be taken to combat the excessive constipation induced by morphine, and it is often advisable to combine the morphine with atropine. Pain over the liver may to some extent be relieved by the local application of a plaster made up of the pharmacopoeial plasters of opium and of belladonna. Hot fomentations or poultices may be given a trial. The application of a belt may give considerable relief. The pain and tenderness are, of course, aggravated by examination, which should, therefore, not be unnecessarily repeated.

For itching, salts of calcium by the mouth, warm alkaline baths, bathing the skin with carbolic acid 1 : 40, or the hypodermic injection of pilocarpine, may give relief; probably morphine will be most generally successful (*vide* p. 567).

Vomiting should be treated by ice, morphine, bismuth, and dilute hydrocyanic acid. Washing out the stomach may be very useful. Flatulence and distension of the intestine should be treated by various carminatives, by minute doses ($\frac{1}{10}$ gr.) of calomel, guaiacol, creosote perles, and by gentle purges. As there may be diminution in the hydrochloric acid of the gastric juice, dilute nitro-hydrochloric acid (Mx) should be given after food. Constipation should be met by saline purges and mild laxatives, such as cascara.

The diet is largely determined by the patient's inclinations; usually there is want of appetite and dislike for meat, so that liquid food, milk, jellies, tea, and coffee are all that he cares to take. Milk has the advantage of being easily digested and giving rise to a minimum of putrefactive products. Stimulants are usually desirable.

If ascites gives rise to abdominal distension and discomfort, tapping should be performed.

→ **Operative Treatment.**—Removal of the growth is, of course, the ideal treatment, but is only to be thought of for a primary and single growth. A number of cases have been operated upon and excision of the malignant growth performed.

In a tabular statement of 76 cases in which resection of the liver had been performed for growths or other conditions,¹ Keen gives 18 carcinomas, 5 sarcomas, and 1 endothelioma. Yeoman² collected 9 cases of excision of primary carcinoma of the liver.

Excision of a primary malignant growth from the substance of the liver is much more difficult than removal of malignant disease of the gall-bladder. Another practical difficulty is that of arriving with any certainty at a diagnosis of a primary hepatic growth before it has become too extensive for satisfactory removal.

Success is, therefore, more likely to occur in cases in which the exploratory operation was undertaken under the idea that there were conditions other than malignant disease present, such as a hydatid cyst. It is very probable that good results might follow in cases in which a small secondary growth is excised at the same time as a primary carcinoma of the stomach or of the gall-bladder, as in Mayo Robson's case³ in which complete recovery followed, is removed, or in the rare cases in which a single metastatic growth occurs in the liver after removal of the primary growth elsewhere. But in such cases there is, unfortunately, the danger of the liver being more widely infected than appears to the naked eye.

Cullen⁴ reported temporary improvement after removal of a secondary growth, undertaken seventeen months after removal of the left kidney for carcinoma.

Laparotomy, with a view of removing a diagnosed growth, would often be only an exploratory incision, for the extent of the disease and the presence of secondary growths would, in a large number of cases, render any operative treatment impracticable. At the present time, however, the value of resection of the liver for new growths is likely to be more extensively tested. Most of the cases that have been operated upon have died from a recurrence of the growth.

¹ Keen. *Ann. Surg.*, 1899, xxx, 276.

² Yeoman. *Journ. Am. Med. Assoc.*, Chicago, 1909, lii, 1741.

³ Mayo Robson. *Med.-Chir. Trans.*, Lond., 1896, lxxix, 159.

⁴ Cullen. *Journ. Am. Med. Assoc.*, Chicago, 1905, xlv, 1239.





